SEVENTH EDITION

PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS

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limits the time during which the product may be dispensed by the pharmacist or used by the patient.

Prescriptions requiring extemporaneous compounding by the pharmacist do not require the extended shelf-life that commercially manufactured and distributed products do because they are intended to be used immediately on their receipt by the patient and used only during the immediate course of the prescribed treatment. However, these compounded prescriptions must remain stable and efficacious during the course of their use and the compounding pharmacist must employ formulative components and techniques which will result in a stable product (7).

In years past pharmacists were confronted primarily with innocuous, topical prescriptions that required extemporaneous formulation. However, in recent years there has been a need to compound other drug delivery systems as well, e.g., progesterone vaginal suppositories, oral suspensions, from existing tablets or capsules. When presented with a prescription that requires extemporaneous compounding, the pharmacist is confronted with a difficult situation because the potency and the stability of these prescriptions is a serious matter. Occasionally, the results of compatibility and stability studies on such prescriptions are published in scientific and professional journals. These are very useful; however, there are also prescriptions for which stability and compatibility information is not readily available. In these instances, it behooves the pharmacist to at least contact the drug manufacturer of the active ingredient(s) to solicit stability information. Also, a compilation of published stability information is included in Trissel's Stability of Compounded Formulations (8). The published stability data are applicable only to products that are prepared identically to the products that are reported.

USP guidelines on stability of extemporaneous compounded formulations state that, in the absence of stability information that is applicable to a specific drug and preparation, the following guidelines can be utilized: nonaqueous liquids and solid formulations where the manufactured drug is the source of the active ingredient-not later than 25% of the time remaining until the product's expiration date or 6 months, whichever is earlier; nonaqueous liquids and solid formulations where a USP or NF substance is the source of active ingredient—a beyond-use date of 6 months; for water-containing formulations prepared from ingredients in solid form—a beyond-use date of not later than 14 days when stored at cold temperatures; for all other formulations—a beyond-use date of the intended duration of therapy or 30 days, whichever is earlier (9). Thus, in the instance where an oral aqueous liquid preparation is made from an existing tablet or capsule formulation, the pharmacist should make up only at most a 14 days supply and it must be stored in a refrigerator. Further, the pharmacist must also dispense the medication in a container conducive to stability and use and must advise the patient of the proper method of use and conditions of storage of the medication.

Finally, when compounding on the basis of extrapolated or less than concrete information it is best for the pharmacist to keep the formulation simple and not to shortcut but use the necessary pharmaceutical adjuvants to prepare the prescription.

Pharmaceutic Ingredients

Definitions and Types

To prepare a drug substance into a final dosage form, pharmaceutic ingredients are required. For example, in the preparation of pharmaceutic solutions, one or more *solvents* are used to dissolve the drug substance, *flavors and sweeteners* are used to make the product more palatable, *colorants* are added to enhance product appeal, *preservatives* may be added to prevent microbial growth and *stabilizers*, such as antioxidants and chelating agents, may be used to prevent drug decomposition, as previously discussed. In the preparation of tablets, *diluents* or *fillers* are commonly added to increase the bulk of the formulation, *binders* to cause the adhesion of the powdered drug and pharmaceutic substances, *antiadherents* or *lubricants* to assist the smooth tableting process, *disintegrating agents* to promote tablet break-up after administration, and coatings to improve stability, control disintegration, or to enhance appearance. Ointments, creams, and suppositories achieve their characteristic features due to the pharmaceutic bases which are utilized. Thus, for each dosage form, the pharmaceutic ingredients establish the primary features of the product, and contribute to the physical form, texture, stability, taste and overall appearance.

Table 3.3 presents the principal categories of pharmaceutic ingredients, with examples of some of the official and commercial agents currently used. Additional discussion of many of the pharmaceutic ingredients may be found in the chapters where they are most relevant; for example, pharmaceutic materials used in tablet and capsule formulations

Table 3.3. Examples of Pharmaceutic Ingredients

Ingredient Type	*Definition*	*Examples*
Acidifying Agent	Used in liquid preparations to provide acidic medium for product stability.	Citric acid Acetic acid Fumaric acid Hydrochloric acid Nitric acid
Alkalinizing Agent	Used in liquid preparations to provide alkaline medium for product stability.	Ammonia solution Ammonium carbonate Diethanolamine Monoethanolamine Potassium hydroxide Sodium borate Sodium carbonate Sodium hydroxide Triethanolamine Trolamine
Adsorbent	An agent capable of holding other molecules onto its surface by physical or chemical (chemisorption) means.	Powdered cellulose Activated charcoal Carbon dioxide
Aerosol Propellant	Agent responsible for developing the pressure within an aerosol container and expelling the product when the valve is opened.	Dichlorodifluoromethane Dichlorotetrafluoroethane Trichloromonofluoromethane
Air Displacement	Agent employed to displace air in a hermetically sealed container to enhance product stability.	Nitrogen Carbon dioxide
Antifungal Preservative	Used in liquid and semi-solid preparations to prevent the growth of fungi. The effectiveness of the parabens is usually enhanced when they are used in combination.	Butylparaben Ethylparaben Methylparaben Benzoic acid Propylparaben Sodium benzoate Sodium propionate
Antimicrobial Preservative	Used in liquid and semi-solid preparations to prevent the growth of microorganisms.	Benzalkonium chloride Benzethonium chloride Benzyl alcohol Cetylpyridinium chloride Chlorobutanol Phenol Phenylethyl alcohol Phenylmercuric nitrate Thimerosal
Antioxidant	Agent that inhibits oxidation and thus is used to prevent the deterioration of preparations by the oxidative process.	Ascorbic acid Ascorbyl palmitate Butylated hydroxyanisole Butylated hydroxytoluene Hypophophorous acid Monothioglycerol Propyl gallate Sodium ascorbate Sodium bisulfite Sodium formaldehyde Sulfoxylate Sodium metabisulfite
Buffering Agent	Used to resist change in pH upon dilution or addition of acid or alkali. potassium metaphosphate	Potassium phosphate, monobasic Sodium acetate Sodium citrate anhydrous and dihydrate

continued

Table 3.3. Examp

Ingredient Type
Chelating Agent
Colorant
Clarifying Agent *Emulsifying Agent*
Encapsulating Agent
Flavorant
Humectant
Levigating Agent
Ointment Base
Plasticizer
Solvent

Table 3.3. Examples of Pharmaceutic Ingredients

Ingredient Type	*Definition*	*Examples*
Chelating Agent	Substance that forms stable, water soluble complexes (chelates) with metals. Chelating agents are used in some liquid pharmaceuticals as stabilizers to complex heavy metals which might promote instability. In such use they are also called *sequestering* agents.	Edetic acid Edetate disodium
Colorant	Used to impart color to liquid and solid (e.g., tablets and capsules) pharmaceutical preparations.	FD&C Red No. 3 FD&C Red No. 20 FD&C Yellow No. 6 FD&C Blue No. 2 D&C Green No. 5 D&C Orange No. 5 D&C Red No. 8 Caramel Ferric oxide, red
Clarifying Agent	Used as a filtering aid because of adsorbent qualities.	Bentonite
Emulsifying Agent	Used to promote and maintain the dispersion of finely subdivided particles of a liquid in a vehicle in which it is immiscible. The end product may be a liquid emulsion or semisolid emulsion (e.g., a cream).	Acacia Cetomacrogol Cetyl alcohol Glyceryl monostearate Sorbitan monooleate Polyoxyethylene 50 stearate
Encapsulating Agent	Used to form thin shells for the purpose of enclosing a drug substance or drug formulation for ease of administration.	Gelatin Cellulose acetate phthalate
Flavorant	Used to impart a pleasant flavor and often odor to a pharmaceutical preparation. In addition to the natural flavorants listed, many synthetic flavorants are also used.	Anise oil Cinnamon oil Cocoa Menthol Orange oil Peppermint oil Vanillin
Humectant	Used to prevent the drying out of preparations—particularly ointments and creams—due to the agent's ability to retain moisture.	Glycerin Propylene glycol Sorbitol
Levigating Agent	Liquid used as an intervening agent to reduce the particle size of a drug powder by grinding together, usually in a mortar.	Mineral oil Glycerin
Ointment Base	Semisolid vehicle into which drug substances may be incorporated in preparing medicated ointments.	Lanolin Hydrophilic ointment Polyethylene glycol ointment Petrolatum Hydrophilic petrolatum White ointment Yellow ointment Rose water ointment
Plasticizer	Used as a component of film-coating solutions to enhance the spread of the coat over tablets, beads, and granules.	Diethyl phthalate Glycerin
Solvent	An agent used to dissolve another pharmaceutic substance or a drug in the preparation of a solution. The solvent may be aqueous or nonaqueous (e.g., oleaginous). Cosolvents, such as water and alcohol (hydroalcoholic) and water and glycerin, may be used when needed. Solvents rendered sterile are used in certain preparations (e.g., injections).	Alcohol Corn oil Cottonseed oil Glycerin Isopropyl alcohol Mineral oil Oleic acid Peanut oil Purified water Water for injection Sterile water for injection Sterile water for irrigation

continued

Examples
acid
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ric acid
ochloric acid
acid
onia solution
onium carbonate
anolamine
oethanolamine
ssium hydroxide
um borate
um carbonate
ium hydroxide
hanolamine
amine
dered cellulose
ivated charcoal
bon dioxide
hlorodifluoromethane
hlorotetrafluoroethane
hloromonofluoromethane
rogen
rbon dioxide
tylparaben
ylparaben
ethylparaben
nzoic acid
opylparaben
dium benzoate
dium propionate
nzalkonium chloride
nzethonium chloride
enzyl alcohol
etylpyridinium chloride
hlorobutanol
henol
henylethyl alcohol
henylmercuric nitrate
himerosal
Ascorbic acid
Ascorbyl palmitate
Butylated hydroxyanisole
Butylated hydroxytoluene
Hypophophorous acid
Monothioglycerol
Propyl gallate
Sodium ascorbate
Sodium bisulfite
Sodium formaldehyde Sulfoxylate
Sodium metabisulfite
Potassium phosphate, monobasic
Sodium acetate
Sodium citrate anhydrous and dihydrate

continued

Table 3.3. Examples of Pharmaceutic Ingredients

Ingredient Type	*Definition*	*Examples*
Stiffening Agent	Used to increase the thickness or hardness of a pharmaceutical preparation, usually an ointment.	Cetyl alcohol Cetyl esters wax Microcrystalline wax Paraffin Stearyl alcohol White wax Yellow wax
Suppository Base	Used as a vehicle into which drug substances are incorporated in the preparation of suppositories.	Cocoa butter Polyethylene glycols (mixtures)
Surfactant (surface active agent)	Substances that absorb to surfaces or interfaces to reduce surface or interfacial tension. May be used as wetting agents, detergents or emulsifying agents.	Benzalkonium chloride Nonoxynol 10 Oxtoxynol 9 Polysorbate 80 Sodium lauryl sulfate Sorbitan monopalmitate
Suspending Agent	A viscosity increasing agent used to reduce the rate of sedimentation of (drug) particles dispersed throughout a vehicle in which they are not soluble. The resultant suspensions may be formulated for use orally, parenterally, ophthalmically, topically, or by other routes.	Agar Bentonite Carbomer (e.g., Carbopol) Carboxymethylcellulose sodium Hydroxyethyl cellulose Hydroxypropyl cellulose Hydroxypropyl methylcellulose Kaolin Methylcellulose Tragacanth Veegum
Sweetening Agent	Used to impart sweetness to a preparation.	Aspartame Dextrose Glycerin Mannitol Saccharin sodium Sorbitol Sucrose
Tablet Antiadherents	Agents that prevent the sticking of tablet formulation ingredients to punches and dies in a tableting machine during production.	Magnesium stearate Talc
Tablet Binders	Substances used to cause adhesion of powder particles in tablet granulations.	Acacia Alginic acid Carboxymethylcellulose sodium Compressible sugar (e.g., Nu-Tab) Ethylcellulose Gelatin Liquid glucose Methylcellulose Povidone Pregelatinized starch
Tablet and Capsule Diluent	Inert substances used as fillers to create the desired bulk, flow properties, and compression characteristics in the preparation of tablets and capsules.	Dibasic calcium phosphate Kaolin Lactose Mannitol Microcrystalline cellulose Powdered cellulose Precipitated calcium carbonate Sorbitol Starch

continued

Table 3.3. Examples of Pharmaceutic Ingredients

Ingredient Type	*Definition*	*Examples*
Tablet Coating Agent	Used to coat a formed tablet for the purpose of protecting against drug decomposition by atmospheric oxygen or humidity, to provide a desired release pattern for the drug substance after administration, to mask the taste or odor of the drug substance, or for aesthetic purposes. The coating may be of various types, including sugar-coating, film coating, or enteric coating. Sugar coating is water-based and results in a thickened covering around a formed tablet. Sugar-coated tablets generally start to break up in the stomach. A film coat is a thin cover around a formed tablet or bead. Unless it is an enteric coat, the film coat will dissolve in the stomach. An enteric-coated tablet or bead will pass through the stomach and break up in the intestines. Some coatings that are water-insoluble (e.g., ethylcellulose) may be used to coat tablets and beads to slow the release of drug as they pass through the gastrointestinal tract.	
Sugar coating:		Liquid glucose Sucrose
Film coating:		Hydroxyethyl cellulose Hydroxypropyl cellulose Hydroxypropyl methylcellulose Methylcellulose (e.g., Methocel) Ethylcellulose (e.g., Ethocel) Cellulose acetate phthalate Shellac (35% in alcohol, ("pharmaceutical glaze")
Enteric coating:		
Tablet Direct Compression Excipient	Used in direct compression tablet formulations.	Dibasic calcium phosphate (e.g., Ditab)
Tablet Disintegrant	Used in solid dosage forms to promote the disruption of the solid mass into smaller particles which are more readily dispersed or dissolved.	Alginic acid Carboxymethylcellulose calcium Microcrystalline cellulose (e.g., Avicel) Polacrilin potassium (e.g., Amberlite) Sodium alginate Sodium starch glycollate Starch
Tablet Glidant	Agents used in tablet and capsule formulations to improve the flow properties of the powder mixture.	Colloidal silica Cornstarch Talc
Tablet Lubricant	Substances used in tablet formulations to reduce friction during tablet compression.	Calcium stearate Magnesium stearate Mineral oil Stearic acid Zinc stearate
Tablet/Capsule Opaquant	Used to render a capsule or a tablet coating opaque. May be used alone or in combination with a colorant.	Titanium dioxide
Tablet Polishing Agent	Used to impart an attractive sheen to coated tablets.	Carnauba wax White wax
Tonicity Agent	Used to render a solution similar in osmotic dextrose characteristics to physiologic fluids. Ophthalmic, parenteral, and irrigation fluids are examples of preparations in which tonicity is a consideration.	Sodium chloride

continued

Table 3.3. Examples of Pharmaceutic Ingredients

Ingredient Type	*Definition*	*Examples*
Vehicle	A carrying agent for a drug substance. They are used in formulating a variety of liquid dosage for oral and parenteral administration. Generally, oral liquids are aqueous preparations (as syrups) or hydroalcoholic (as elixirs). Parenteral solutions for intravenous use are aqueous, whereas intramuscular injections may be aqueous or oleaginous.	
Flavored/Sweetened		Acacia Syrup Aromatic Syrup Aromatic Elixir Cherry Syrup Cocoa Syrup Orange Syrup Syrup
Oleaginous		Corn Oil Mineral Oil Peanut Oil Sesame Oil
Sterile		Bacteriostatic Sodium chloride injection Bacteriostatic Water for Injection
Viscosity Increasing Agent	Used to change the consistency of a preparation to render it more resistant to flow. Used in suspensions to deter sedimentation, in ophthalmic solutions to enhance contact time (e.g., methylcellulose), to thicken topical creams, etc.	Alginic acid Bentonite Carbomer Carboxymethylcellulose Sodium Methylcellulose Povidone Sodium alginate Tragacanth

are discussed in Chapter 7, Capsules and Tablets and Chapter 8, Modified-Release Dosage Forms and Drug Delivery Systems.

Handbook of Pharmaceutical Excipients

The reader should also be aware of the *Handbook of Pharmaceutical Excipients* (10), which presents monographs on over 200 excipients used in pharmaceutical dosage form preparation. Included in each monograph is such information as: nonproprietary, chemical, and commercial names; empirical and chemical formulas and molecular weight; pharmaceutic specifications and chemical and physical properties; incompatibilities and interactions with other excipients and drug substances; regulatory status; and applications in pharmaceutic formulation or technology.

Harmonization of Standards

There is great interest currently in the international "harmonization" of standards applicable to pharmaceutical excipients. This is due to the fact that the pharmaceutical industry is multinational, with major companies having facilities in more than a single country, with products sold in markets worldwide, and with regulatory approval for these products required in each individual country. Standards for each drug substance and excipient used in pharmaceuticals are contained in pharmacopeias—or, for new agents, in an application for regulatory approval by the FDA or another nation's governing authority. The four pharmacopeias with the largest international use are the *United States Pharmacopeia/National Formulary* (USP/NF), *British Pharmacopeia* (BP), *European Pharmacopeia* (EP), and the *Japanese Pharmacopeia* (JP). Uniform standards for excipients in these and other pharmacopeias

7

CAPSULES AND TABLETS

Chapter at a Glance

WHEN MEDICATIONS are to be administered orally to adults, capsules and tablets usually are preferred because they are conveniently carried, readily identified, and easily taken.

Consider the convenience of a patient carrying a day's, week's, or month's supply of capsules or tablets compared with equivalent doses of a liquid medication. With capsules and tablets as dosing units, there is no need for spoons or other measuring devices, which sometimes may be inconvenient and may result in less than accurate dosing. Also, most capsules and tablets are tasteless when swallowed, which is not the case with oral liquid medication.

The characteristic shapes and colors of capsules and tablets and the manufacturer's name and product code number commonly embossed or imprinted on their surface make them readily identified. This enhances communications between the patient and health care providers, assists patient compliance, and fosters safe and effective medication use.

Capsules and tablets are available for many medications in a variety of dosage strengths thereby providing prescribing flexibility to the prescriber and accurate individualized dosage for the patient. Some tablets are *scored*, or grooved, which allows them to be easily broken into two or more parts. This enables the patient to swallow smaller portions as may be desired, or when prescribed, it allows the tablet to be taken in reduced or divided dosage. Tablets that are not scored are not intended to be broken or cut by the patient since they may have special coatings and/or drug-release features that would be compromised by altering the tablet's physical integrity.

From a pharmaceutic standpoint, solid dosage forms are efficiently and productively manufactured; they are packaged and shipped by manufacturers at lower cost and with less breakage than comparable liquid forms; and are more stable and have a longer shelf-life than their liquid counterparts.

As discussed later in this chapter, empty hard gelatin capsules are often used by the pharmacist in the extemporaneous compounding of prescriptions. On occasion, a pharmacist may use commercially available capsules and tablets as the *source* of a medicinal agent when it is not otherwise available. In these instances, the pharmacist must take into account any excipients that are present in the commercial product to ensure compatibility with the other ingredients in the compounded prescription. Capsules and tablets designed to provide modified drug release are discussed in Chapter 8.

Capsules

Capsules are solid dosage forms in which medicinal agents and/or inert substances are enclosed within a small shell of gelatin. Gelatin capsule shells may be *hard* or *soft* depending on their composition.

The vast majority of filled capsules are intended to be swallowed whole by the patient for the benefit of the medication contained therein. However, it is not unusual practice in hospitals and extended care facilities for a caregiver to open capsules or crush tablets to mix with food or drink, especially for children or other patients unable to swallow solid dosage forms. This should be done only with the concurrence of the pharmacist since the drug release characteristics of certain dosage forms could be altered and adversely affect the patient's welfare.

Dosage forms that must be left intact include: enteric coated tablets, designed to pass through the stomach for drug release and absorption in the intestine; extended-release dosage forms, designed to provide prolonged release of the medication; and sublingual or buccal tablets, formulated to dissolve under the tongue or in the oral cavity (1). In instances in which a patient is unable to swallow an intact solid dosage form, an alternative product, such as a chewable tablet, instant dissolving tablet, oral liquid, suppository or injection may be employed.

Hard Gelatin Capsules

Hard gelatin capsule shells are used to manufacture most of the commercially available medicated capsules. They are also commonly employed in clinical drug trials, to compare the effects of an investigational drug to another drug product or placebo. Hard gelatin capsules also are used by the community pharmacist in the extemporaneous compounding of prescriptions. The empty capsule shells are made from a mixture of gelatin, sugar and water. As such, they are clear, colorless, and essentially tasteless. They may be colored with various FD&C and D&C dyes and may be made opaque by adding agents such as titanium dioxide. Most commercially available medicated capsules contain combinations of colorants and opaquants to make them distinctive, many with caps and bodies of different colors.

Gelatin is obtained by the partial hydrolysis of collagen obtained from the skin, white connective tissue, and bones of animals. In commerce, it is available in the form of a fine powder, a coarse powder, shreds, flakes, or sheets (Fig. 7.1).

Gelatin is stable in air when dry but is subject to microbial decomposition when it becomes moist.

Fig. 7.1 *Pork* s
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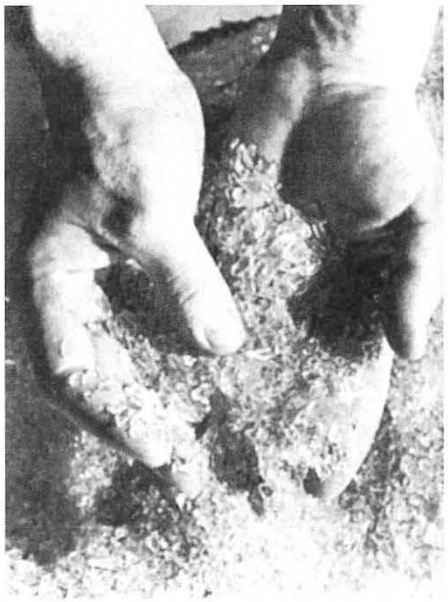

Fig. 7.1 *Pork skin gelatin used as raw material in the manufacture of gelatin capsules. (Courtesy of SmithKline Beecham.)*

Normally, hard gelatin capsules contain between 13 and 16% of moisture (2). However, if stored in an environment of high humidity, additional moisture is absorbed by the capsules, and they may become distorted and lose their rigid shape. In an environment of extreme dryness, some of the moisture normally present in the gelatin capsules is lost and the capsules may become brittle and crumble when handled. Therefore, it is desirable to maintain hard gelatin capsules in an environment free from excess humidity or dryness.

Because moisture may be absorbed by gelatin capsules and affect hygroscopic agents contained within, many capsules are packaged along with a small packet of a desiccant material to protect against the absorption of atmospheric moisture. The desiccant materials most used are dried silica gel, clay, and activated carbon.

Prolonged exposure to high humidity can affect *in vitro* capsule dissolution. Such changes have been observed in capsules containing tetracycline, chloramphenicol, and nitrofurantoin (3). Because such changes could forewarn of possible changes in bioavailability, capsules subjected to such stress conditions must be evaluated on a case by case basis (3).

Although gelatin is insoluble in cold water, it does soften through the absorption of up to ten times its weight of water. Some patients prefer to swallow a capsule wetted with water or saliva because a wetted capsule slides down the throat more readily than a dry capsule. Gelatin is soluble in hot water and in warm gastric fluid a gelatin capsule rapidly dissolves and exposes its contents. Gelatin, being a protein, is digested by proteolytic enzymes and absorbed.

A number of methods have been developed to track the passage of capsules and tablets through the gastrointestinal tract to map their transit time and drug-release patterns. Among these is gamma *scintigraphy*, a noninvasive procedure which involves use of a gamma ray-emitting radiotracer incorporated into the formulation with a gamma camera coupled to a data recording system (4–5). The quantity of material added to allow gamma scintigraphy is small and does not compromise the usual in vivo characteristics of the dosage form being studied. When scintigraphy is combined with pharmacokinetic studies, the resultant *pharmacoscintographic* evaluation provides information of the transit and drug release patterns of the dosage form as well as the rate of drug absorption from the various regions of the gastrointestinal tract (4). This method is particularly useful in: (a) identifying whether a correlation exists between in vitro and in vivo bioavailability for immediate-release products; (b) assessing the integrity and transit time of enteric coated tablets through the stomach enroute to the intestines; and (c) drug/dosage form evaluation in new product development (4–5). A separate technique, using a pH-sensitive, nondigestible, radiotelemetric device termed the Heidelberg capsule, the approximate size of a No. 0 gelatin capsule, has been used as a *non*radioactive means to measure gastric pH, gastric residence time, and gastric emptying time of solid dosage forms in fasting and nonfasting human subjects (6).

As discussed in Chapter 4, drug absorption from the gastrointestinal tract depends on a number of factors, including the solubility characteristics of the drug substance, the type of product formulation (i.e., immediate-release, modified-release, enteric coated), the gastrointestinal contents and intersubject differences in physiologic character and response.

The Manufacture of Hard Gelatin Capsule Shells

Hard gelatin capsule shells are manufactured in two sections, the capsule body and a shorter cap. The two parts overlap when joined, with the cap fitting snugly over the open end of the capsule body.

The shells are produced industrially by the mechanical dipping of pins or pegs of the desired shape and diameter into a temperature-controlled reservoir of melted gelatin mixture (Figs. 7.2, 7.3). The pegs, made of manganese bronze, are affixed to plates, each capable of holding up to about 500 pegs. Each plate is mechanically lowered to the gelatin bath, the pegs submerged to the desired depth and maintained for the desired period to achieve the proper length and thickness of coating. Then the plate and the pegs are slowly lifted from the bath and the gelatin dried by a gentle flow of temperature- and humidity-controlled air. When dried, each capsule part is trimmed mechanically to the proper length, removed from the pegs and the capsule bodies and caps are joined together. It is important that the thickness of the gelatin walls be strictly controlled so that the capsule's body and cap fit snugly to prevent disengagement. The pegs on which the caps are formed are slightly larger in diameter than the pegs on which the bodies are formed, allowing the telescoping of the caps over the bodies. In capsule shell production, there is a continuous dipping, drying, removing and joining of capsules as the peg-containing plates are rotated in and out of the gelatin bath. As noted earlier, capsule shells may be made distinctive by adding colorants and/or opaquants to the gelatin bath.

A manufacturer also may prepare distinctive-looking capsules by altering the usual rounded shape of the capsule-making pegs. By tapering the end of the body-producing peg while leaving the cap-making peg rounded, one manufacturer prepares capsules differentiated from those of other manufacturers (PULVULES, Eli Lilly). Another manufacturer utilizes capsules with the ends of both the bodies and caps highly tapered (SPANSULE Capsules, SmithKline Beecham). Yet another innovation in capsule shell design is the SNAP-FIT, CONI-SNAP, and CONI-SNAP SUPRO hard gelatin capsules depicted in Figures 7.4 and 7.5. The original SNAP-FIT construction enables the two halves of the capsule shells to be positively joined through locking grooves in the shell walls. The two grooves fit into each other and thus ensure reliable closing of the filled capsule. During the closing process, the capsule body is inserted into the cap. With the high-capacity filling rates of the modern capsule filling machines (over 180,000 capsules per hour), capsule splitting ("telescoping") and/or denting of the capsule shell occurs with the slightest contact between the two capsule-part rims when they are joined. This problem, which exists primarily with straight-walled capsule shells, led to the development of the CONI-SNAP capsule, in which the rim of the capsule body is not straight, but tapered slightly (Fig. 7.5). This reduces the risk of the capsule-rims touching on joining, and essentially

Fig. 7.2 *Body of capsules and their caps are shown as they move through automated capsule-making machine. Each machine is capable of producing 30,000 capsules per hour. It takes a 40-minute cycle to produce a capsule. (Courtesy of SmithKline Beecham.)*

Fig. 7.3 *Capsu*
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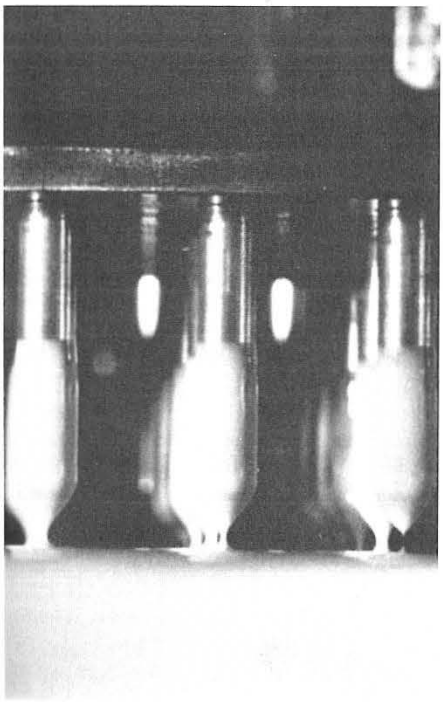


Fig. 7.3 *Capsules being dipped for coloring on automated capsule-making equipment. (Courtesy of SmithKline Beecham.)*

eliminates the problem of splitting during large-scale filling operations. In the CONI-SNAP SUPRO capsules, the upper capsule part extends so far over the lower part that only the rounded edge of the latter is visible (Fig. 7.5). Opening of such a filled capsule is difficult because the lower surface offers less gripping surface to pull the two halves apart. This increases the security of the contents and the integrity of the capsule.

After filling, some manufacturers render their capsules tamper-evident through various capsule sealing techniques. These methods are discussed later in this section. Capsules and tablets also may be imprinted with the names or monograms of the manufacturer, the assigned national drug code (NDC) number and other markings making the product identifiable and distinguishable from other products (Fig. 7.6).

Capsule Sizes

Empty gelatin capsules are manufactured in various sizes, varying in length, in diameter, and capacity. The size selected for use is determined by the amount of fill material to be encapsulated. The density and compressibility of the fill will largely determine to what extent it may be packed into a capsule shell (7). For estimation, a comparison may be made with powders of well-known features (Table 7.1) and an initial judgment made as to the approximate capsule size needed to hold a specific amount of material. However, the final determination largely may be the result of trial. For human use, empty capsules ranging in size from 000 (the largest) to 5 (the smallest) are commercially available (Fig. 7.7). Larger capsules are available for veterinary use.

For prescriptions requiring extemporaneous compounding, hard gelatin capsules permit a wide prescribing latitude by the physician. The pharmacist may compound capsules of a single medicinal agent or combination of agents at the precise dosage prescribed for the individual patient.

Preparation of Filled Hard Gelatin Capsules

The large-scale or small-scale preparation of filled hard gelatin capsules is divided into the following general steps.

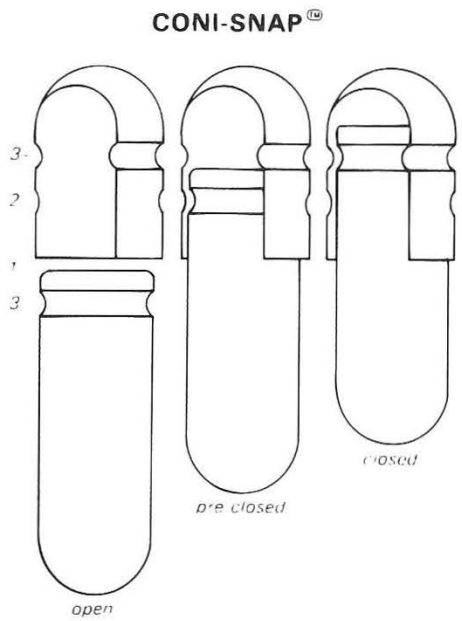


Fig. 7.4 *Line drawings of the CONI-SNAP capsule in open, pre-closed, and closed positions. The tapered rims 1) avoid telescoping; the indentations 2) prevent premature opening, and the grooves 3) lock the two capsule parts together after the capsule has been filled. (Courtesy of Capsugel Division, Warner-Lambert Co.)*

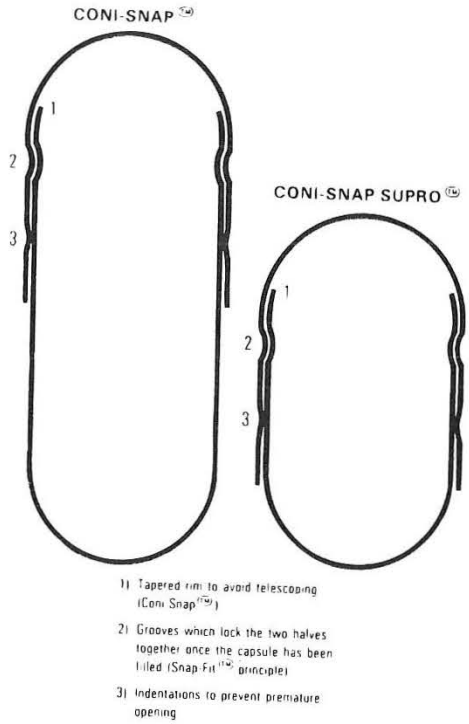


Fig. 7.5 *Line drawings of the CONI-SNAP and CONI-SNAP SUPRO (on right) capsules. The latter is designed to be smaller and to have the lower portion of the capsule shell concealed except for the rounded end. This makes separation of the two parts more difficult and contributes to capsule integrity. (Courtesy of Capsugel Division, Warner-Lambert Co.)*

1. Developing and preparing the formulation and selecting the size capsule.
2. Filling the capsule shells.
3. Capsule sealing (optional).
4. Cleaning and polishing the filled capsules.

Developing the Formulation and Selection of Capsule Size

In developing a capsule formulation, the goal is to prepare a capsule with accurate dosage, good bioavailability, ease of filling and production, stability, and elegance.

In dry formulations, the active and inactive components must be blended thoroughly to ensure a uniform powder mix for the capsule fill. Care in blending is especially critical for low-dose drugs since lack of homogeneity could result in significant therapeutic consequences. Preformulation studies are performed to determine if all of the formulation's bulk powders may be effectively blended together as such or if they require reduction of particle size or other processing to achieve homogeneity.

A diluent or filler may be added to the formulation to produce the proper capsule fill volume. Lactose, microcrystalline cellulose and starch are commonly used for this purpose. In addition to providing bulk, these materials often provide cohesion to the powders, which is beneficial in the transfer of the powder blend into capsule shells (2). Disintegrants are frequently included in a capsule formulation to assist the break-up and distribution of the capsule contents in the stomach. Among the disintegrants used are pregelatinized starch, croscarmellose, and sodium starch glycolate.

To achieve uniform drug distribution, it is advantageous if the density and particle size of the drug and nondrug components are similar. This is par-

Fig. 7.6 *Examples of tablets and capsules marked with a letter-number code to facilitate identification. (Courtesy of Eli Lilly and Company.)*

Table 7.1. Approximate Capacity of Empty Gelatin Capsules

	Capsule Size							
Volume (mL)	*1.40*	*0.95*	*0.68*	*0.50*	*0.37*	*0.30*	*0.21*	*0.13*
*Drug Substance (mg)**								
Quinine Sulfate	650	390	325	227	195	130	97	65
Sodium Bicarbonate	1430	975	715	510	390	325	260	130
Aspirin	1040	650	520	325	260	195	162	97

*Amount may vary according to the degree of pressure used in filling the capsules.

ticularly important when a drug of low dosage is blended with other drugs or nondrug fill (8). When necessary, particle size may be reduced by *milling* to produce particles ranging from about 50 to 1000 microns. Milled powders may be blended effectively for uniform distribution throughout a powder mix when the drug's dosage is 10 mg or greater (8). For drugs of lower dose or when smaller particles are required, *micronization* is employed. Depending on the materials and equipment used, micronization produces particles ranging from about 1 to 20 microns in size.

In preparing capsules on an industrial scale using high-speed automated equipment, the powder mix or granules must be free-flowing to allow steady passage of the capsule fill from the hopper through the encapsulating equipment and into the capsule shells. The addition of a *lubricant or glidant* such as fumed silicon dioxide, magnesium stearate, calcium stearate, stearic acid, or talc (about 0.25–1%) to the powder mix enhances flow properties (2).

When magnesium stearate is used as the lubricant, the water-proofing characteristics of this water-insoluble material can retard penetration by the gastrointestinal fluids and delay drug dissolution and absorption. The addition of surface active agents, as sodium lauryl sulfate, to capsule and tablet formulations is used to facilitate wetting by the gastrointestinal fluids to overcome the problem (9). Even in instances in which a water-insoluble lubricant is not used, after the gelatin capsule shell dissolves, gastrointestinal fluids must displace the air that surrounds the dry powder and penetrate the drug before it can be dispersed and dissolved. Powders of poorly soluble drugs have a tendency to resist such penetration. Disintegration agents included in a capsule formulation facilitate the break up and distribution of the capsule's contents.

Whether it be the presence of a lubricant, surfactant, disintegrating agent, or some other pharmaceutic excipient, formulation can influence the bioavailability of a drug substance and can account for differences in drug effects, which may be encountered between two capsule products of the same medicinal substance. Pharmacists must be aware of this possibility when product-interchange is considered.

Inserting tablets or small capsules within capsules is sometimes a useful technique in the commercial production of capsules and in a pharmacist's extemporaneous preparation of capsules (Fig. 7.8). This may be done to separate chemically incompatible agents or to add premeasured (as tablets) amounts of potent drug substances. Rather

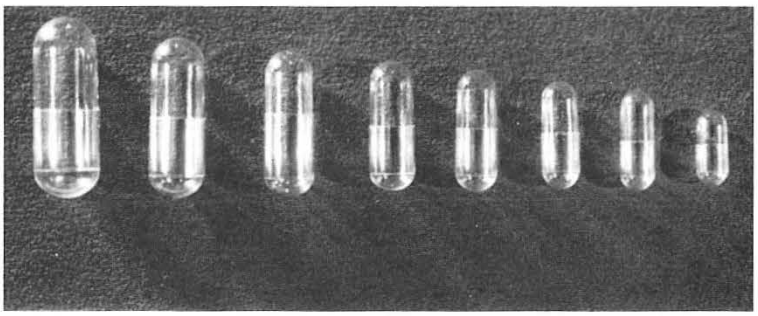


Fig. 7.7 *Actual sizes of hard gelatin capsules. From left to right, sizes 000, 00, 0, 1, 2, 3, 4, and 5.*

Fig. 7.8 *Examples of fill in hard gelatin capsules. 1, powder or granulate; 2, pellet mixture; 3, paste; 4, capsule; and 5, tablet. (Courtesy of Capsugel, Division of Warner-Lambert)*

than weighing a potent drug, a pharmacist may choose to insert an available prefabricated tablet of the desired strength in each capsule. Other less potent agents and diluents may then we weighed and added. On an industrial scale, coated pellets designed for modified-release drug delivery are also commonly placed in capsule shells.

Gelatin capsules are unsuitable for the encapsulation of aqueous liquids because water softens gelatin and distorts the capsules, resulting in leakage of the contents. However, some liquids such as fixed or volatile oils that do not interfere with the stability of the gelatin shells may be placed in locking gelatin capsules (or the capsules may be sealed with a solution of gelatin thinly coating the interface of the cap and body) to ensure the retention of the liquid. Rather than placing a liquid in a capsule as such, the liquid may be mixed with an inert powder to make a wetted mass or paste, which may then be placed in capsules in the usual manner (Fig. 7.8). *Eutectic mixtures* of drugs, or mixtures of agents that have a propensity to liquefy when admixed, may be mixed with a diluent or absorbent such as magnesium carbonate, kaolin, or light magnesium oxide to separate the interacting agents and to absorb any liquefied material which may form.

In large-scale capsule production, liquids are placed in *soft gelatin* capsules that are sealed during the filling and manufacturing process. Soft capsules are discussed later in this chapter.

In most instances the amount of drug placed in a capsule represents a single dose of the medication. In some instances, when the usual dose of the drug is too large to place in a single capsule, two or more capsules may be required to provide the desired dose. The total amount of formula prepared is that amount necessary to fill the desired number of capsules. On an industrial scale this means hundreds of thousands of capsules. In community practice, an individual prescription may call for the preparation of only six or a dozen capsules. Any slight loss in fill-material during the preparation and capsule-filling process will not materially affect an industrial size batch, but in the community pharmacy, a slight loss of powder would result in an inadequate quantity to fill the last capsule. To ensure enough fill in the compounding of small numbers of capsules, the community pharmacist may calculate for the preparation of one or two more capsules than is required to fill the prescription. However, this procedure may not be followed for capsules containing a controlled substance since the amount of drug used and that called for in the prescription must strictly coincide.

The selection of the capsule size for a commercial product is done during the product development stage. The choice is determined by requirements of the formulation, including the dose of the active ingredient, and the density and compaction characteristics of the drug and nondrug components. If the dose of the drug is inadequate to fill the volume of the capsule body, a diluent is added. Information on the density and compaction characteristics of a capsule's active and inactive components and comparison to other similar materials and prior experiences can serve as a guide in selecting capsule size (7).

Hard gelatin capsules are used to encapsulate between about 65 mg and 1 g of powdered material. As shown in Table 7.1, the smallest capsule (No. 5), may be expected to hold 65 mg of powder or more, depending on the characteristics of the powder substance. Oftentimes, in the extemporaneous compounding of prescriptions, the best capsule size to use is determined by trial. Use of the smallest size capsule, properly filled, is preferred. A properly filled

capsule should have its body filled with the drug mixture, not the cap. The cap is intended to fit snugly over the body to retain the contents.

The following examples demonstrate the drug and nondrug contents of a few commercially available capsules.

Tetracycline Capsules

Active ingredient:	Tetracycline hydrochloride, 250 mg
Filler:	Lactose
Lubricant/glidant:	Magnesium stearate
Capsule colorants:	FD&C Yellow No. 6, D&C Yellow No. 10, D&C Red No. 28, FD&C Blue No. 1
Capsule opaquant:	Titanium dioxide

Acetaminophen with Codeine Capsules

Active ingredients:	Acetaminophen, 325 mg Codeine phosphate, 30 mg
Disintegrant:	Sodium starch glycolate
Lubricant/glidants:	Magnesium stearate, stearic acid
Capsule colorants:	D&C Yellow No. 10, Edible Ink, FD&C Blue No. 1 (FD&C Green No. 3 and FD&C Red No. 40)

Diphenhydramine Hydrochloride Capsules

Active ingredient:	Diphenhydramine HCl, 50 mg
Filler:	Confectioner's sugar
Lubricants/glidants:	Talc, colloidal silicon dioxide
Wetting agent:	Sodium lauryl sulfate
Capsule colorants:	FD&C Blue No. 1, FD&C Red No. 3
Capsule opaquant:	Titanium dioxide

Filling Hard Capsule Shells

When filling a small number of capsules in the pharmacy, the pharmacist uses the "punch" method. In this method, the pharmacist takes the precise number of empty capsules to be filled from his stock container. By counting the capsules as the initial step rather than taking a capsule from stock as each one is filled, the pharmacist guards against filling an erroneous number of capsules and avoids contaminating the stock container with drug powder. The powder to be encapsulated is placed on a sheet of clean paper or on a glass or porcelain plate. Using the spatula, the powder mix is formed into a cake having a depth of approximately one-fourth to one-third the length of the capsule body. Then an empty capsule body is held between the thumb and forefinger and "punched" vertically into the powder cake repeatedly until filled. Some pharmacists wear surgical gloves or latex finger cots to avoid handling the capsules with bare fingers. Because the amount of powder packed into a capsule depends upon the degree of compression, the pharmacist should punch each capsule in the same manner and after capping weigh the product. When nonpotent materials are placed in capsules, the first filled capsule should be weighed (using an empty capsule of the same size on the opposite balance pan to counter the weight of the shell) to determine the capsule size to use and the degree of compaction to be used. After this determination, the other capsules should be prepared and weighed periodically to check the uniformity of the process. When potent drugs are being used, *each capsule* should be weighed after filling to ensure accuracy. Such weighings protect against the uneven filling of capsules and the premature exhaustion or underutilization of the powder. After the body of a capsule has been filled and the cap placed on the body, the body may be squeezed gently to distribute some powder to the cap-end to give the capsule a full appearance.

Granular material that does not lend itself to the "punch" method of filling capsules may be poured into each capsule individually from the powder paper on which it is weighed.

Pharmacists who prepare capsules on a regular or extensive basis may use hand-operated capsule filling machines (Fig. 7.9). The various types of available machines have capacities ranging from 24 to 300 capsules and when efficiently operated are capable of producing from about 200 to 2000 capsules per hour.

Machines developed for industrial use automatically separate the caps from empty capsules, fill the bodies, scrape off the excess powder, replace the caps, seal the capsules as desired, and clean the outside of the filled capsules at a rate of up to 165,000 capsules per hour (Fig. 7.10). The formulation must be such that the filled body contains the accurate drug dosage. This is verified through the use of automated in-process sampling and analysis equipment and processes (Figs. 7.11, 7.12).

As described later, the USP requires adherence to standards for *content uniformity* and *weight variation* for capsules to assure the accuracy of dosage units.

Capsule Sealing

As mentioned previously, some manufacturers make tamper-evident capsules by sealing the joint between the two capsule parts. One manufacturer

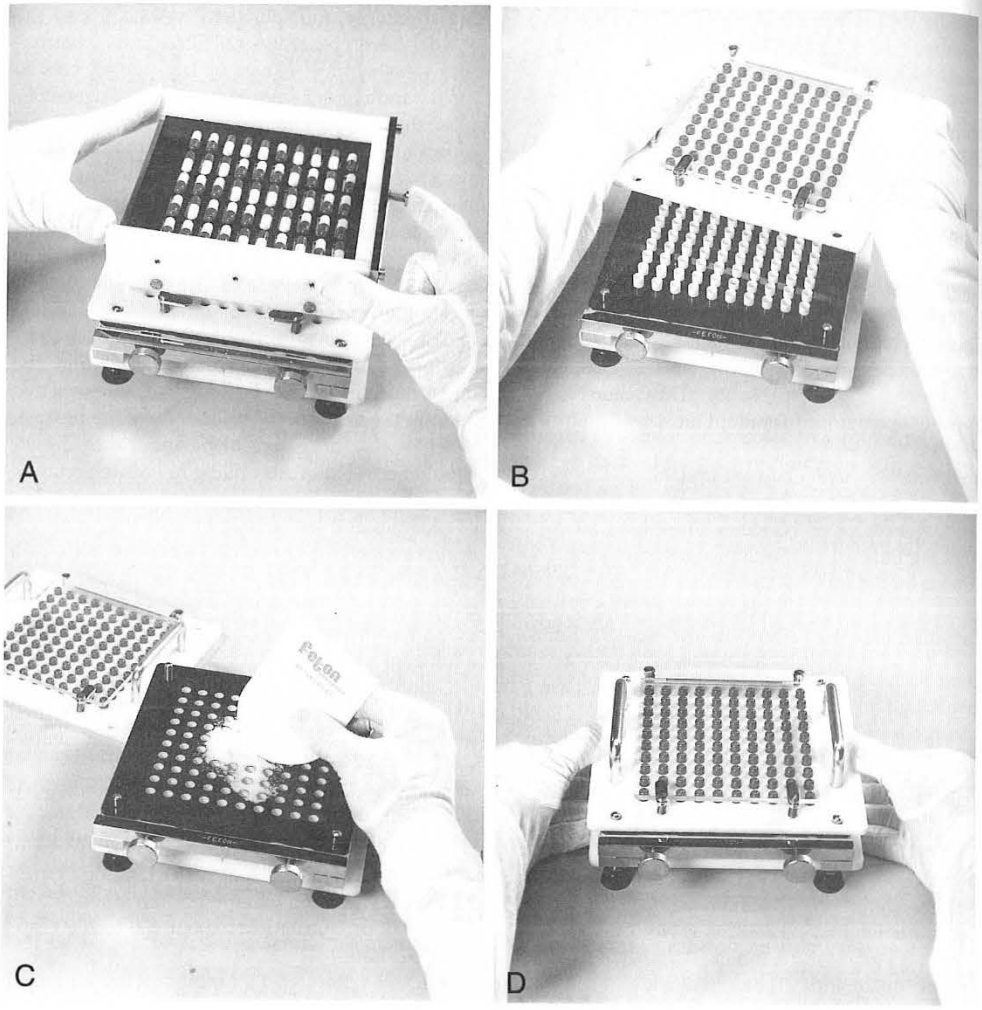


Fig. 7.9 *The Feton capsule filling machine. A, with empty capsules in the loader tray, the tray placed on top of the filler unit; B, the loader inserts the capsules into the filling unit and is removed and the top plate is lifted to separate the caps from the bodies; C, the powder is placed on the unit and the capsule bodies filled; D, the top plate then is returned to the unit and the caps placed on filled capsule bodies. (Courtesy of Chemical and Pharmaceutical Industry Company)*

makes distinctive-looking capsules by sealing them with a colored band of gelatin (KAPSEALS, Parke-Davis). If removed, the band cannot be restored without expert resealing with gelatin. Capsules may also be sealed through a heat welding process that fuses the capsule cap to the body through the double wall thickness at their juncture (10). The process results in a distinctive "ring" around the capsule where heat welded. Still another process utilizes a melting-point-lowering liquid wetting agent in the contact areas of the capsule's cap and body and then thermally bonds the two parts using low temperatures (40–45°C) (11). Industrial capsule sealing machines are capable of producing 60,000 to 150,000 gelatin banded, heat welded, or thermally coupled capsules per hour (12). Figure 7.13 depicts a sealed hard gelatin capsule. Although difficult and tedious, extemporaneously prepared

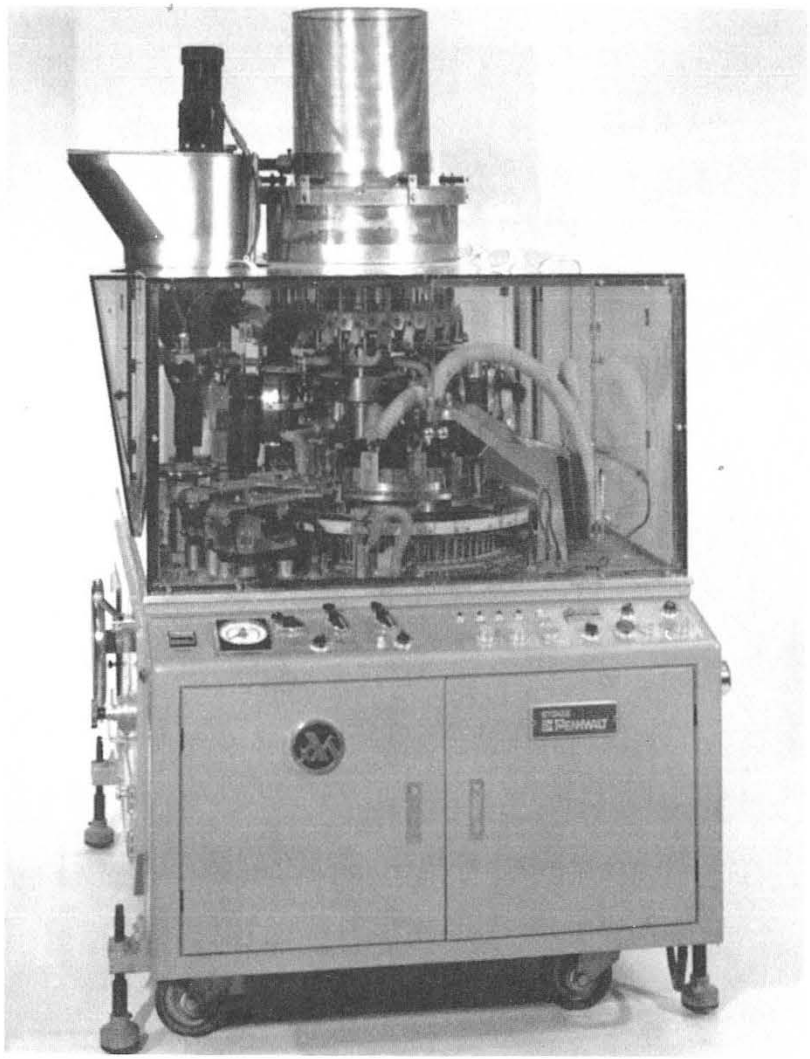


Fig. 7.10 *Osaka Automatic Capsule Filler (Model R-180), capable of filling up to 165,000 capsules per hour. (Courtesy of Sharples-Stokes Div., Stokes-Merrill, Pennwalt Corporation.)*

capsules may be sealed by lightly coating the inner surface of the cap with a warm gelatin solution immediately prior to placement on the filled capsule body.

Cleaning and Polishing Capsules

Small amounts of powder may adhere to the outside of capsules after filling. The powder may be bitter or otherwise unpalatable and should be removed before packaging or dispensing. On a small scale, capsules may be cleaned individually or in small numbers by rubbing them with a clean gauze or cloth. On a large scale, many capsule-filling machines are affixed with a cleaning vacuum that removes any extraneous material from the capsules as they exit the equipment. Figure 7.14 shows the industrial cleaning and polishing of hard filled capsules using the Accela-Cota apparatus.

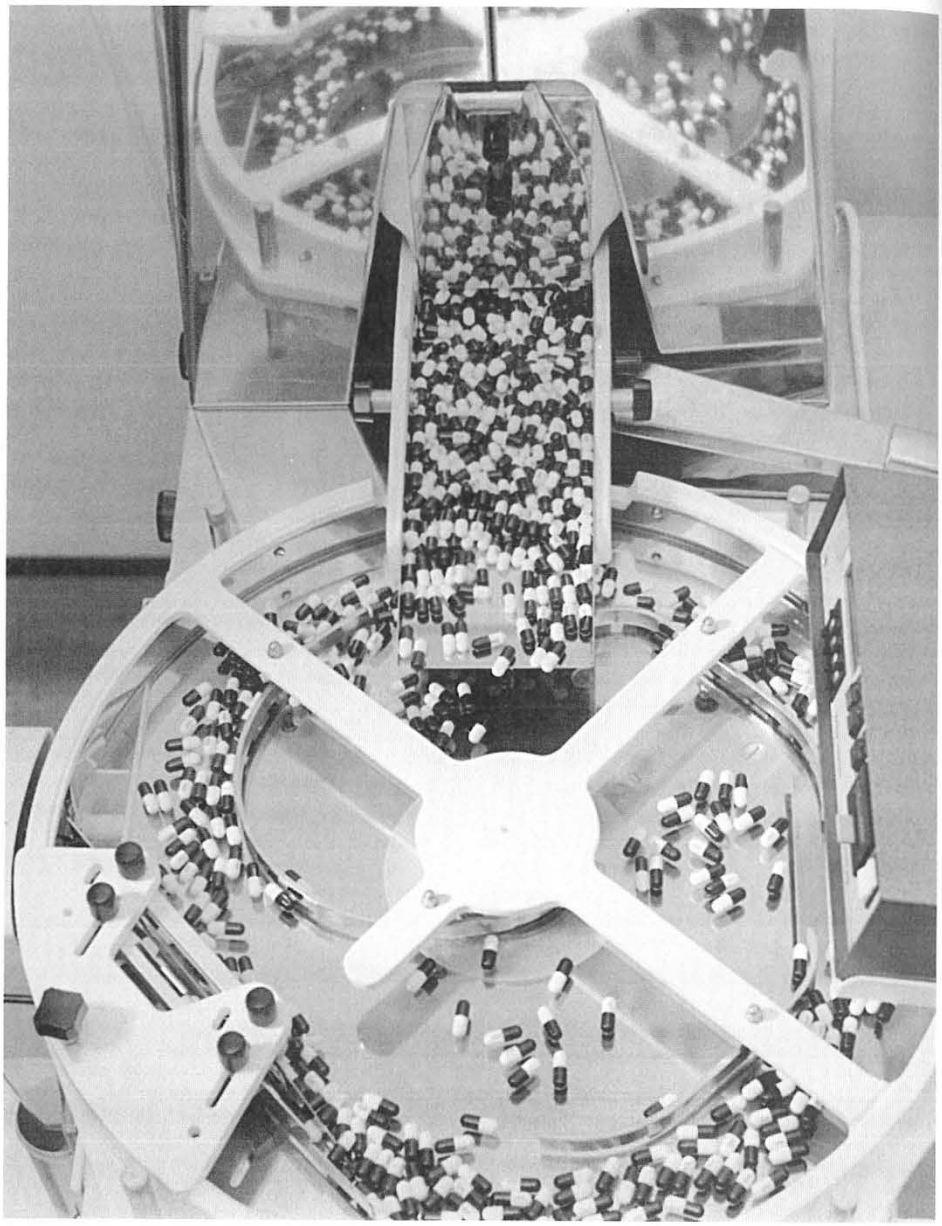


Fig. 7.11 *Automatic capsule weighing apparatus, Vericap 1800 A Checkweigher, which rejects capsules not having the precise weight. (Courtesy of Elan Corporation)*

Soft Gelatin Capsules

Soft gelatin capsules are made of gelatin to which glycerin or a polyhydric alcohol such as sorbitol has been added to render the gelatin elastic or plastic-like. Soft gelatin capsules, which contain more moisture than hard capsules, may have a preservative added as methylparaben and/or propylparaben to retard microbial growth. Soft gelatin capsules may be manufactured to be oblong, oval or round

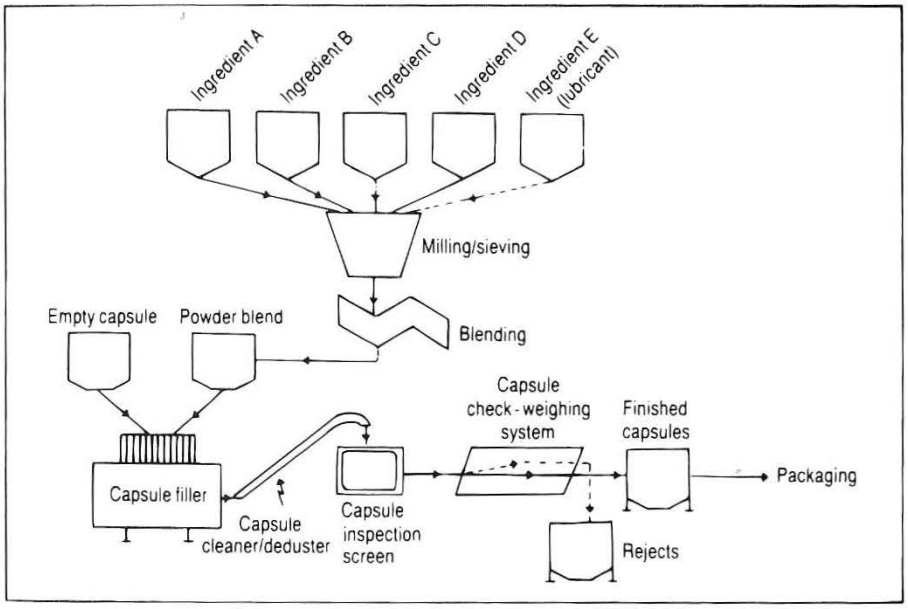


Fig. 7.12 *Process flow diagram for automated capsule filling. (Reprinted with permission from Yelvig M. Principles of process automation for liquid and solid dosage forms. Pharm Technol, 8:47, 1984.)*

in shape. They may be prepared of a single or two-tone color and may be imprinted with identifying markings. As hard gelatin capsules, they may be prepared with opaquants to reduce transparency and render characteristic feature to the capsule shell.

Soft gelatin capsules are used to hermetically seal and encapsulate liquids, suspensions, pasty materials, dry powders and even preformed tablets. Soft gelatin capsules are pharmaceutically elegant and are easily swallowed by the patient.

Fig. 7.13 *Z-Weld's gelatin seal fuses the two capsule halves together to create a one-piece capsule that is tamper-evident. (Courtesy of Raymond Automation Co.)*

Preparation of Soft Gelatin Capsules (13)

They may be prepared by the plate process, using a set of molds to form the capsules, or by the more efficient and productive rotary or reciprocating die processes by which they are produced, filled, and sealed in a continuous operation (Fig. 7.15).

By the plate process, a warm sheet of plain or colored gelatin is placed on the bottom plate of the

Fig. 7.14 *Cleaning and polishing hard filled capsules using the Accela-Cota apparatus. (Courtesy of Eli Lilly and Company.)*

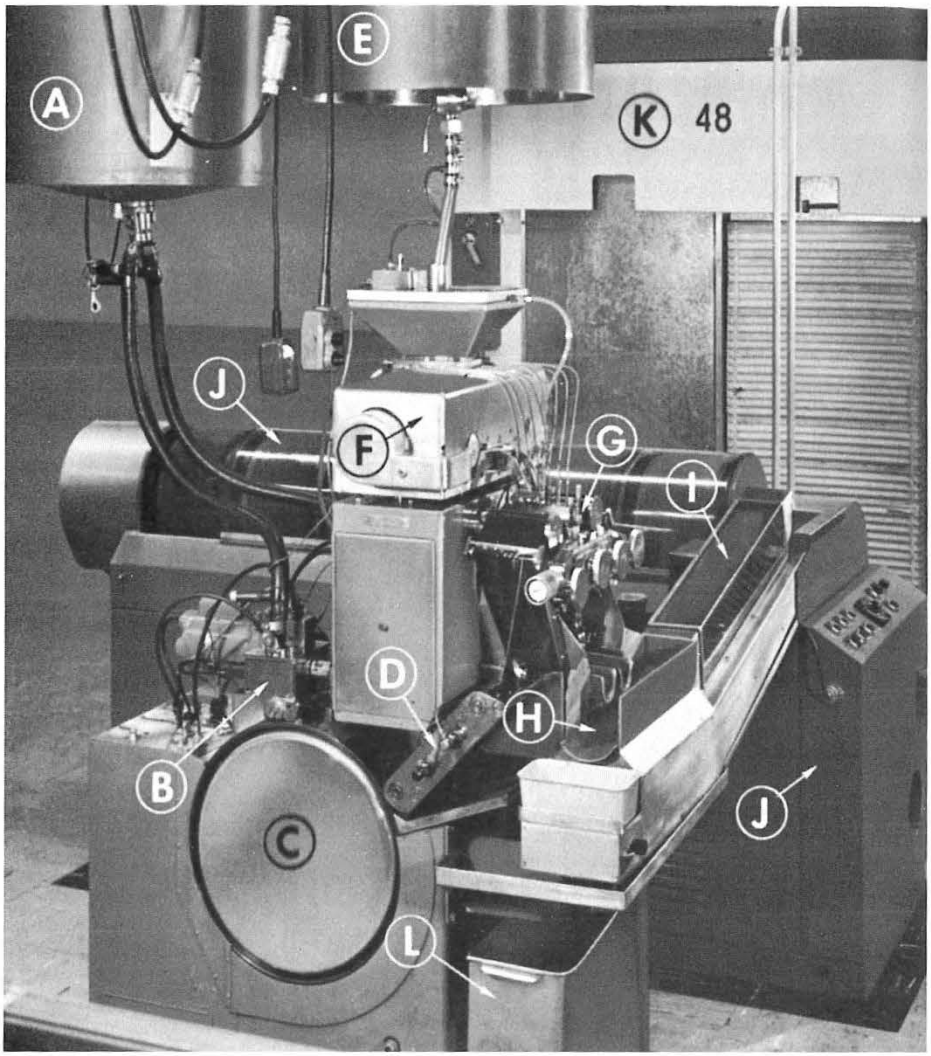
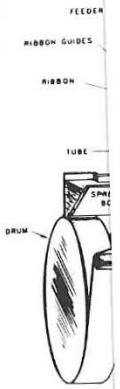


Fig. 7.15 *Rotary die process equipment. A, Gelatin tank; B, spreader box; C, gelatin ribbon casting drum; D, mineral oil lubricant bath; E, medicine tank; F, filling pump; G, encapsulating mechanism; H, capsule conveyor; I, capsule washer; J, infrared dryer; K, capsule drying tunnel; L, gelatin net receiver. (Courtesy of R.P. Scherer Corporation.)*

mold and the liquid-containing medication is evenly poured on it. Then a second sheet of gelatin is carefully placed on top of the medication and the top plate of the mold is put into place. Pressure is then applied to the mold to form, fill, and seal the capsules simultaneously. The capsules are removed and washed with a solvent harmless to the capsules.

Most soft gelatin capsules are prepared by the rotary die process, a method developed in 1933 by Robert P. Scherer. By this method, liquid gelatin flowing from an overhead tank is formed into two continuous ribbons by the rotary die machine and brought together between twin rotating dies (Fig. 7.16). At the same time, metered fill material is injected between the ribbons precisely at the moment that the dies form pockets of the gelatin ribbons. These pockets of fill-containing gelatin are sealed by pressure and heat and then severed from



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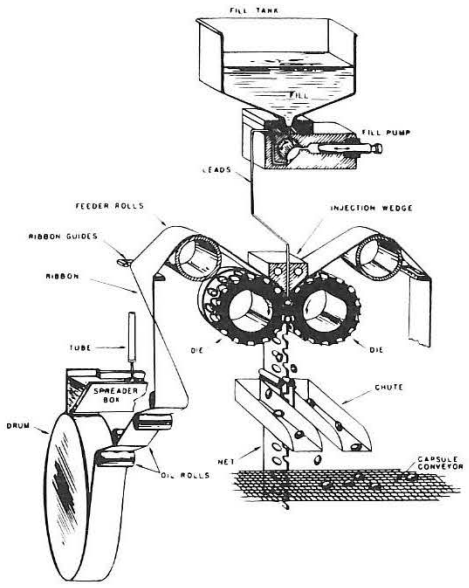

Fig. 7.16 *Schematic drawing of rotary die process. (Courtesy of R.P. Scherer Corporation.)*

the ribbon. Use of ribbons of two different colors results in bicolored capsules.

The reciprocating die process is similar to the rotary process in that ribbons of gelatin are formed and used to encapsulate the fill, but it differs in the actual encapsulating process. The gelatin ribbons are fed between a set of vertical dies that continually open and close to form rows of pockets in the gelatin ribbons. These pockets are filled with the medication and are sealed, shaped, and cut out of the film as they progress through the machinery. As the capsules are cut from the ribbons, they fall into refrigerated tanks which prevent the capsules from adhering to one another.

Utilization of Soft Gelatin Capsules

Soft gelatin capsules are prepared to contain a variety of liquid, pasty, and dry fills. Liquids that may be encapsulated into soft gelatin capsules include the following (13):

1. Water-immiscible volatile and nonvolatile liquids such as vegetable and aromatic oils, aromatic and aliphatic hydrocarbons, chlorinated hydrocarbons, ethers, esters, alcohols and organic acids.
2. Water-miscible, nonvolatile liquids, such as polyethylene glycols, and nonionic surface active agents as polysorbate 80.
3. Water-miscible and relatively nonvolatile compounds, as propylene glycol and isopropyl alcohol, depending on factors as concentration used and packaging conditions.

Liquids that can easily migrate through the capsule shell cannot be encapsulated into soft gelatin capsules. These materials include water above 5%, and low molecular weight water-soluble and volatile organic compounds such as alcohols, ketones, acids, amines, and esters.

Solids may be encapsulated into soft gelatin capsules as solutions in a suitable liquid solvent, suspensions, dry powders, granules, pellets, or small tablets.

Compendial Requirements for Capsules

Added Substances

Substances added to official preparations, including capsules, to enhance their stability, usefulness, elegance, or to facilitate their manufacture, may be used only if they (14):

1. are harmless in the quantities used;
2. do not exceed the minimum amounts required to provide their intended effect;
3. do not impair the product's bioavailability, therapeutic efficacy or safety, and
4. do not interfere with requisite compendial assays and tests.

Containers for Dispensing Capsules

There are specifications listed in the USP prescribing the type of container suitable for the repackaging or dispensing of each official capsule and tablet. Depending on the item, the container might be required to be *tight, well-closed and light resistant.*

Disintegration Test for Capsules

The compendial disintegration test for hard and soft gelatin capsules follows the same procedure and uses the same apparatus described later in this chapter for uncoated tablets. The capsules are placed in the basket-rack assembly, which is repeatedly immersed 30 times per minute into a thermostatically controlled fluid at 37°C and observed over the time described in the individual monograph. To fully satisfy the test, the capsules disinte-

grate completely into a soft mass having no palpably firm core, and only some fragments of the gelatin shell.

Dissolution Test for Capsules

The compendial dissolution test for capsules uses the same apparatus, dissolution medium and test as that for uncoated and plain coated tablets described later in this chapter. However, in instances in which the capsule shells interfere with the analysis, the contents of a specified number of capsules can be removed and the empty capsule shells dissolved in the dissolution medium before proceeding with the sampling and chemical analysis.

Weight Variation

The uniformity of dosage units may be demonstrated by determining *weight variation* and/or *content uniformity*. The weight variation method is as follows.

HARD CAPSULES. Ten capsules are individually weighed and the contents removed. The emptied shells are individually weighed and the net weight of the contents calculated by subtraction. From the results of an assay performed as directed in the individual monograph, the content of active ingredient in each of the capsules is determined.

SOFT CAPSULES. The gross weight of 10 intact capsules is determined individually. Then each capsule is cut open with a scissors or a sharp open blade, and the contents removed by washing with a suitable solvent. The solvent is allowed to evaporate at room temperature over a period of about 30 minutes, taking precautions to avoid uptake or loss of moisture. The individual shells are weighed and the net contents calculated. From the results of the assay directed in the individual monograph, the content of active ingredient in each of the capsules is determined.

Content Uniformity

Unless otherwise stated in the monograph for an individual capsule, the amount of active ingredient, determined by assay, is within the range of 85% to 115% of the label claim for 9 of 10 dosage units assayed, with no unit outside the range of 70% to 125% of label claim. Additional tests are prescribed when two or three dosage units are outside of the desired range but within the stated extremes.

Content Labeling Requirement

All official capsules must be labeled to express the quantity of each active ingredient in each dosage unit.

Stability Testing

Stability testing of capsules is performed as described in Chapter 3 to determine the intrinsic stability of the active drug molecule and the influence of environmental factors as temperature, humidity, light, formulative components and the container/closure system. The battery of stress testing, long-term stability and accelerated stability tests help determine the appropriate conditions for storage and the product's anticipated shelf-life.

Moisture Permeation Test

The USP requires determination of the moisture-permeation characteristics of single-unit and unit-dose containers to assure their suitability for packaging capsules. The degree and rate of moisture penetration is determined by packaging the dosage unit together with a color-revealing desiccant pellet, exposing the packaged unit to known relative humidity over a specified time, observing the desiccant pellet for color change (indicating absorption of moisture) and comparing the pre- and post-weight of the packaged unit.

Official and Commercially Available Capsules

There are approximately 200 officially recognized medications in capsule form in the USP. However commercially, there are many fold this number of capsule products available from various manufacturers for various drugs and in various dosage strengths.

Examples of official and commercially available medications in hard and soft gelatin capsules are presented in Tables 7.2 and 7.3.

Inspecting, Counting, Packaging, and Storing Capsules

Capsules produced on a small or large scale should be uniform in appearance. Visual or electronic inspection should be undertaken to detect any flaws in the integrity and appearance of the capsules. Defective capsules should be rejected. In commercial manufacture, Current Good Manufacturing Practice regulations require that if the number of production flaws is excessive, the cause must be investigated, documented and steps undertaken to correct the problem.

In the pharmacy, capsules may be counted manually or by automated equipment. For counting small numbers of solid dosage units, specially de-

Table 7.2. Examples of Some Official Capsules

Official Capsule	*Some Representative Commercial Capsules*	*Capsule Strengths*	*Category*
Amoxicillin	Wymox (Wyeth-Ayerst)	250 and 500 mg	Antibacterial
Ampicillin	Omnipen (Wyeth-Ayerst)	250 and 500 mg	Antibacterial
Cephalexin	Keflex (Dista)	250 and 500 mg	Antibacterial
Diphenhydramine HCl	Benadryl HCl (Parke-Davis)	25 and 50 mg	Antihistaminic
Doxycycline Hyclate	Vibramycin (Pfizer)	50 and 100 mg	Antibacterial
Erythromycin Estolate	Ilosone (Dista)	125 and 250 mg	Antibactetrial
Fluoxitine HCl	Prozac (Dista)	10 and 20 mg	Antidepressant
Flurazepam HCl	Dalmane (Roche)	15 and 30 mg	Hypnotic
Gemfibrozil	Lopid (Parke-Davis)	300 mg	Antihyperlipidemic
Griseofulvin	Grisactin (Wyeth-Ayerst)	125 and 250 mg	Antifungal
Indomethacin	Indocin (Merck)	25 and 50 mg	Antiinflammatory; antipyretic; analgesic
Levodopa	Larodopa (Roche)	100, 250, and 500 mg	Antiparkinsonian
Loperamide HCl	Imodium (Janssen)	2 mg	Antidiarrheal
Oxazepam	Serax (Wyeth-Ayerst)	10, 15 and 30 mg	Antianxiety
Propoxyphene HCl	Darvon (Lilly)	32 and 65 mg	Analgesic
Tetracycline HCl	Achromycin V (Lederle)	250 and 500 mg	Antimicrobial

signed trays are used, as the type depicted in Figure 7.17. In using this tray, the pharmacist pours a supply of capsules or tablets from the bulk source onto the clean tray, and using the spatula counts and sweeps the dosage units into the trough until the desired number is reached. Then the pharmacist closes the trough cover, picks up the tray, returns the uncounted dosage units to the bulk container by means of the lip at the back of the tray, places the prescription container at the opening of the trough, and carefully transfers the capsules or tablets into the container. By this method, the dosage units remain untouched by the pharmacist. To prevent batch-to-batch contamination, the tray must be wiped clean after each use because powder, particularly from counting uncoated tablets, may remain.

In some community and hospital pharmacy settings, small automated counting and filling machines may be used as shown in Figure 7.18.

On the industrial scale, solid dosage forms are counted by large automated pieces of equipment that count and transfer the desired number of dosage units into bulk containers. The containers are then mechanically capped, inspected visually or electronically, labeled, and inspected once more. Some filled containers are then placed into outer packaging cartons. An industrial counting and filling machine is shown in Figure 7.19. Capsules are packaged in glass or in plastic containers, some containing packets of a desiccant to prevent the absorption of excessive moisture.

The unit dose and strip packaging of solid dosage

Table 7.3. Examples of Medications Commercially Prepared into Soft Gelatin Capsules

Drug Substance	*Trade Name and Manufacture*	*Contents and Comments**
Acetazolamide	Diamox Sequels (Lederle)	Acetazolamide is a powder which is very slightly soluble in water. The capsules contain coated pellets of the drug with sustained release features. Acetazolamide is a carbonic anhydrase inhibitor.
Cyclosporine	Sandimmune (Novartis)	Cyclosporine is a slightly water soluble crystalline powder. The capsule also contains corn oil and polyoxyethylated glycolyzed glycerides. Cyclosporine in an immunosuppressive agent.
	Neoral (Novartis)	The capsule contains cyclosporine, dehydrated alcohol, corn oil-mono-ditriglycerides, polyoxyl 40 hydrogenated castor oil. The formulation forms a microemulsion in contact with aqueous fluids for enhanced bioavailability.
Digoxin	Lanoxicaps (Glaxo Wellcome)	Digoxin is a practically water-insoluble powder. The drug is dissolved in a solvent of polyethylene glycol 400, ethyl alcohol, propylene glycol and water. Digoxin is a cardiac glycoside.
Ethchlorvynol	Placidyl (Abbott)	Ethchlorvynol is a liquid immiscible in water. It is a hypnotic. The capsules also contain polyethylene glycol and sorbitol.
Ethosuximide	Zarontin (Parke-Davis)	Ethosuximide is a water soluble powder. The capsule also contains polyethylene glycol 400. Ethosuximide is an anticonvulsant.
Ranitidine HCl	Zantac GELdose (Glaxo Wellcome)	Ranitidine HCl is a water soluble granular powder. The drug is in a nonaqueous matrix of synthetic coconut oil and triglycerides. Ranitidine is a histamine H_2-receptor inhibitor.

*Only a partial listing of the capsule contents is given. The soft capsule shells may also contain colorants, opaquants, preservatives, and other agents.

forms, particularly by pharmacies that service nursing homes and hospitals, provides sanitary handling of the medications, ease of identification, and security in accountability for medications. Typical small scale strip packaging equipment and commercial unit-dose packages of capsules and tablets are presented in Figures 7.20 and 7.21, respectively. Capsules should be stored in tightly capped containers in a cool, dry place.

Tablets

Tablets are solid dosage forms usually prepared with the aid of suitable pharmaceutical excipients. They may vary in size, shape, weight, hardness, thickness, disintegration and dissolution characteristics, and in other aspects, depending upon their intended use and method of manufacture. The majority of tablets are used in the oral administration of drugs. Many of these are prepared with colorants and coatings of various types. Other tablets, as those administered sublingually, buccally or vaginally are prepared to have features most applicable to their particular route of administration. Advantages of tablets for oral administration were presented at the outset of this chapter.

Tablets are prepared primarily by compression with a limited number prepared by molding. Compressed tablets are manufactured with tablet machines capable of exerting great pressure in compacting the powdered or granulated tableting material (Fig. 7.22). Their shape and dimensions are determined by use of various shaped punches and dies (Fig. 7.23). Molded tablets are prepared on a large-scale by tablet machinery or on a small-scale by manually forcing dampened powder material

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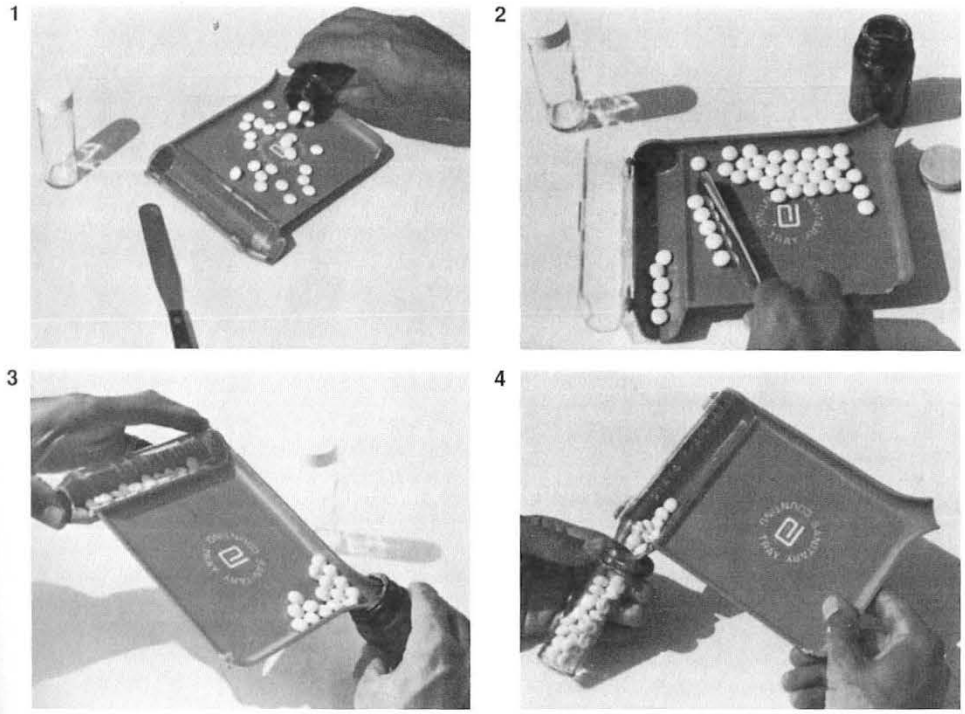

Fig. 7.17 *Steps in the counting of solid dosage units with the Abbott Sanitary Counting Tray: 1) placing units from stock package onto tray, 2) counting and transferring units to trough, 3) returning excess units to stock container, and 4) placing counted units into prescription container.*

into a mold from which the formed tablet is then ejected and allowed to dry.

Types of Tablets

The various types of tablets are described as follows, with their common abbreviations in parentheses.

Compressed Tablets (C.T.)

In addition to the medicinal agent(s), compressed tablets usually contain a number of pharmaceutical adjuncts including (a) *diluents* or *fillers*, which add the necessary bulk to a formulation to prepare tablets of the desired size; (b) *binders* or *adhesives*, which promote the adhesion of the particles of the formulation, enabling a granulation to be prepared and the maintenance of the integrity of the final tablet; (c) *disintegrants* or *disintegrating agents*, which promote the breakup of the tablets after administration to smaller particles for more ready drug availability; (d) *antiadherents, glidants, lubricants* or

Fig. 7.18 *Versacount Model automatic tablet and capsule counting and filling apparatus. (Courtesy of Production Equipment Co.)*

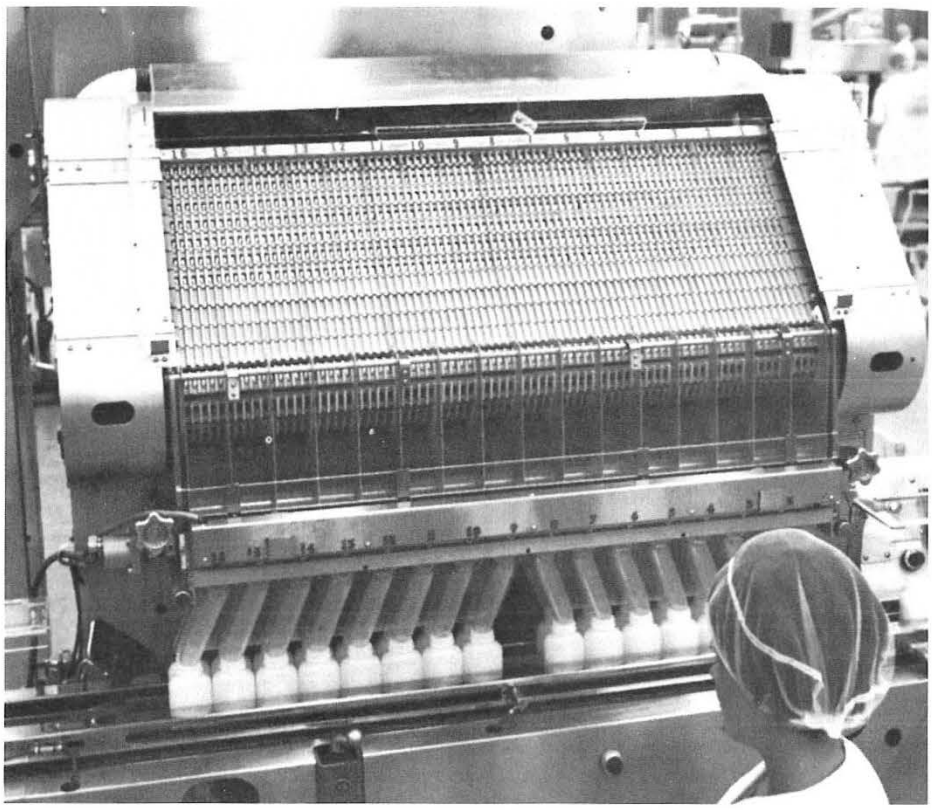

Fig. 7.19 *Large Merrill filling machine that fills 16 bottles with 200 tablets each at one time. A flipper gate in the upper manifold directs the tablets into one row of bottles while the other filled row is evacuated and a new row of bottles moves into place. (Courtesy of The Upjohn Company.)*

lubricating agents, which enhance the flow of the tableting material into the tablet dies, minimize wear of the punches and dies, prevent the sticking of fill material to the punches and dies and produce tablets having a sheen; and (e) *miscellaneous adjuncts* such as colorants and flavorants. After compression, tablets may be coated with various materials as described later. Tablets for oral, buccal, sublingual or vaginal administration may be prepared by compression.

Multiple Compressed Tablets (M.C.T.)

Multiple compressed tablets are prepared by subjecting the fill material to more than a single compression. The result may be a multiple-layered tablet or a tablet-within-a-tablet, the inner tablet being the *core* and the outer portion being the *shell* (Fig. 7.24). Layered tablets are prepared by the initial compaction of a portion of fill material in a die followed by additional fill material and compression to form two- or three-layered tablets, depending upon the number of separate fills. Each layer may contain a different medicinal agent, separated from one another for reasons of chemical or physical incompatibility, staged drug release, or simply for the unique appearance of the multiple-layered tablet. Usually, each portion of fill is colored differently to prepare a distinctive looking tablet. In the preparation of tablets having a compressed tablet as the inner core, special machines are required to place the preformed tablet precisely within the die for the subsequent compression of surrounding fill material.

Sugar-Coated Tablets (S.C.T.)

Compressed tablets may be coated with a colored or an uncolored sugar layer. The coating is water-soluble and is quickly dissolved after swallow-

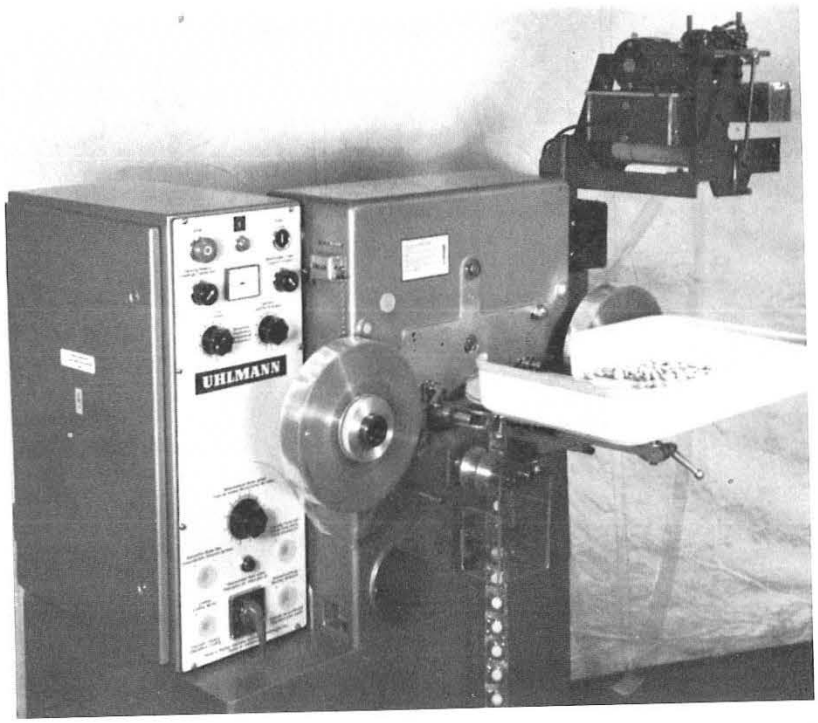

Fig. 7.20 *Strip packager for the unit dose dispensing of solid dosage forms. Drug information is imprinted on each individual package unit. The model shown has a fully automatic cutoff from 1 to 24 dosage units and is especially suited to unit-dose packaging and dispensing in hospitals, dispensaries, nursing homes, and clinics. (Courtesy of Lakso Company, Inc.)*

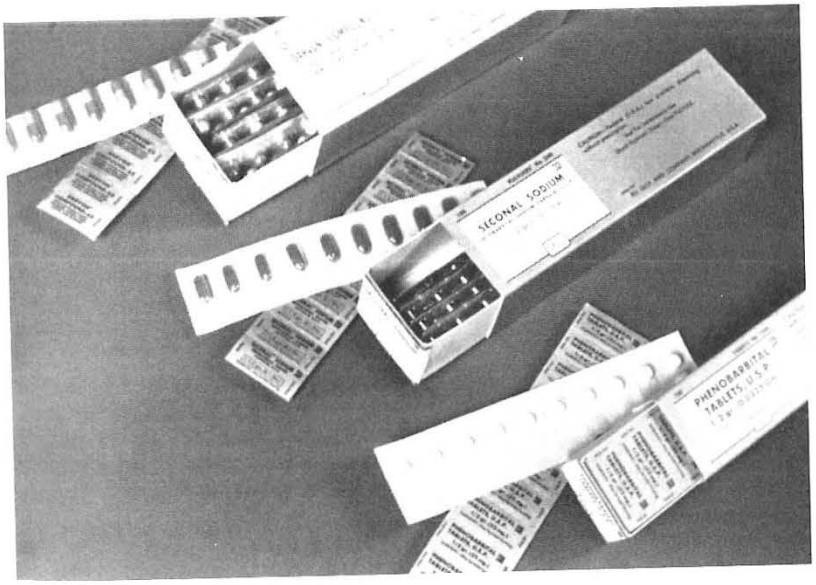

Fig. 7.21 *Example of unit-dose packaging of tablets and capsules. The drug name and other information are imprinted on the backing portion of each unit. (Courtesy of Eli Lilly and Company.)*

Fig. 7.22 *Example of a high-performance double rotary tablet press. The Korsch PharmapressR has a maximum output of 1 million tablets per hour but for continuous operation it is generally run to produce 600,000 to 800,000 tablets per hour. (Courtesy of Korsch Tableting, Inc.)*

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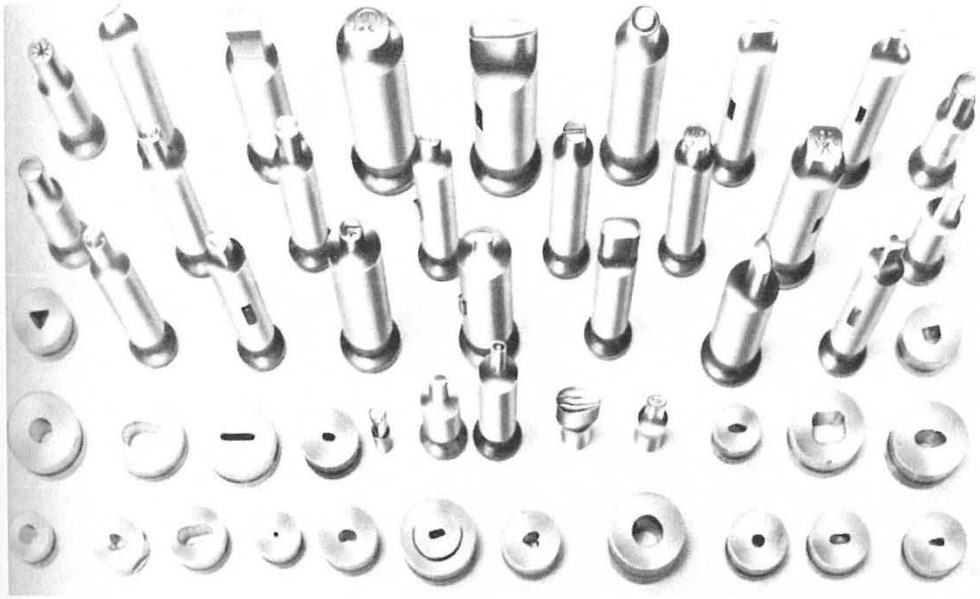

Fig. 7.23 *Various Stokes punches and dies for the production of distinctive tablets. (Courtesy of Stokes Equipment Division, Pennwalt Chemicals Corporation.)*

ing. It serves the purpose of protecting the enclosed drug from the environment and provides a barrier to objectional tasting or smelling drugs. The sugar coating also enhances the appearance of the compressed tablet and permits the imprinting of identifying manufacturer's information. Among the disadvantages to sugar-coating tablets are the time and expertise required in the coating process and the increase in the size, weight, and shipping costs of the tablets. Sugar-coated tablets may be 50% larger and heavier than the original uncoated tablets.

Film-Coated Tablets (F.C.T.)

Film-coated tablets are compressed tablets coated with a thin layer of a polymer capable of forming a skin-like film over the tablet. The film is usually colored and has the advantage over sugar-coatings in that it is more durable, less bulky, and less time-consuming to apply. By its composition, the coating is designed to rupture and expose the core tablet at the desired location within the gastrointestinal tract.

Gelatin-Coated Tablets

A recent innovation in tablet coating is the gelatin-coated tablet. The innovator product, termed GELCAPS, is a capsule-shaped compressed tablet (Fig. 7.25) that allows the coated product to be about one-third smaller than a capsule filled with an equivalent amount of powder. The gelatin coating facilitates swallowing and compared to unsealed capsules, gelatin-coated tablets are more tamper-evident.

Enteric-Coated Tablets (E.C.T.)

Enteric-coated tablets have delayed-release features. They are designed to pass unchanged through

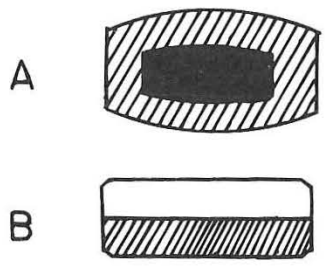

Fig. 7.24 *Diagram of multiple-compressed tablets. A, having a core of one drug and a shell of another, and B, a multiple-layered tablet of two drugs.*

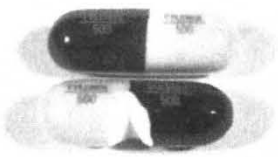

Fig. 7.25 *Cut-away view of "Gelcaps" dosage form. A gelatin-coated capsule-shaped tablet. Dosage form is more easily swallowed than a comparable tablet, smaller than an equivalent capsule, and tamper-evident. (Courtesy of McNeil Consumer Products Co.)*

the stomach with transit to the intestines where the tablets disintegrate and allow drug dissolution and absorption and/or effect. Enteric coatings are employed in instances in which the drug substance is destroyed by gastric acid, is particularly irritating to the gastric mucosa, or when by-pass of the stomach substantially enhances drug absorption.

Buccal or Sublingual Tablets

Buccal or sublingual tablets are flat, oval tablets intended to be dissolved in the buccal pouch (*buccal tablets*) or beneath the tongue (*sublingual tablets*) for absorption through the oral mucosa. They enable the oral absorption of drugs that are destroyed by the gastric juice and/or are poorly absorbed from the gastrointestinal tract. Buccal tablets are designed to erode slowly, whereas those for sublingual use (as nitroglycerin sublingual tablets) dissolve promptly and provide rapid drug effects. *Lozenges* or *troches*, are disc-shaped, solid dosage forms containing a medicinal agent and generally a flavoring substance in a hard candy or sugar base. They are intended to be slowly dissolved in the oral cavity usually for localized effects although some may be formulated for systemic absorption.

Chewable Tablets

Chewable tablets, which have a smooth, rapid disintegration when chewed or allowed to dissolve in the mouth, have a creamy base usually of specially flavored and colored mannitol. Chewable tablets are especially useful for the administration of tablets of large-size to children and adults who have difficulty swallowing solid dosage forms.

Effervescent Tablets

Effervescent tablets are prepared by compressing granular effervescent salts that release gas when in contact with water. These tablets generally contain medicinal substances which dissolve rapidly when added to water.

Molded Tablets (M.T.)

Certain tablets, as tablet triturates, may be prepared by molding rather than by compression. The resultant tablets are very soft, soluble, and are designed for rapid dissolution.

Tablet Triturates (T.T.)

Tablet triturates are small, usually cylindrical, molded (M.T.T.) or compressed tablets (C.T.T.) containing small amounts of usually potent drugs. Today only a few tablet triturate products are available commercially, with most of these produced by tablet compression. Since tablet triturates must be readily and completely soluble in water only a minimal amount of pressure is applied during their manufacture. A combination of sucrose and lactose is usually the diluent. The few tablet triturates which remain are used sublingually, as nitroglycerin tablets.

In the past, pharmacists employed tablet triturates in compounding procedures. For example, they were inserted into capsules or dissolved in liquid preparations to provide accurate amounts of potent drug substances.

Hypodermic Tablets (H.T.)

Hypodermic tablets are no longer available in the United States. They were originally used by physicians in the extemporaneous preparation of parenteral solutions. The required number of tablets was dissolved in a suitable vehicle, sterility attained, and the injection performed. The tablets were a convenience, since they could be easily carried in the physician's medicine bag and injections prepared to meet the needs of the individual patients. However, the difficulty in achieving sterility, the current availability of prefabricated injectable products, some in disposable syringes, have eliminated the need for hypodermic tablets.

Dispensing Tablets (D.T.)

Dispensing tablets are no longer in use. They might better have been termed *compounding tablets* because they were used by the pharmacist in compounding prescriptions and were *not* dispensed as such to the patient. The tablets contained large amounts of highly potent drug substances enabling the pharmacist to rapidly obtain premeasured amounts for compounding multiple dosage units. These tablets had the dangerous potential of being inadvertently dispensed as such to patients.

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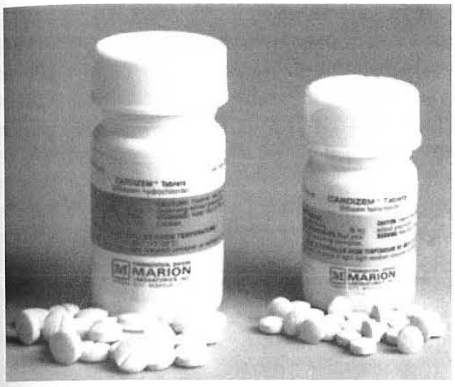

Fig. 7.26 *Packages of a drug product of two different tablet strengths, with one scored for ease of breaking in half. (Courtesy of Marion Laboratories.)*

Immediate Release Tablets (I.R.)

Immediate release tablets are designed to disintegrate and release their medication absent of any special rate-controlling features as special coatings and other techniques.

Instant Disintegrating / Dissolving Tablets

Instant-release tablets are characterized by disintegrating/dissolving in the mouth within one minute; some within 10 seconds [e.g., Claritin Reditabs (loratadine), Schering]. Tablets of this type are designed for pediatric and geriatric patients or for any patient who has difficulty in swallowing tablets. After placing them on the tongue they liquefy and the patient swallows the liquid. A number of techniques are used to prepare these tablets involving lyophilization (e.g., Zydis, R.P. Scherer), soft direct compression (e.g., WOW-Tab, Yamanouchi-Shaklee Pharma), and other methods (e.g., Quicksolv, Janssen). These tablets are prepared using very water-soluble excipients designed to "wick" water into the tablet for rapid disintegration/dissolution. They have the stability characteristics of other solid dosage forms.

Extended Release Tablets (E.R.)

Extended-release tablets (sometimes called "controlled release (CR)" tablets) are designed to release their medication in a predetermined manner over an extended period of time. They are discussed in Chapter 8.

Vaginal Tablets

Vaginal tablets, also called *vaginal inserts*, are uncoated and bullet- or ovoid-shaped tablets which are inserted into the vagina for localized effects. They are prepared by compression and shaped to fit snugly on plastic inserter devices which accompany the product. They contain antibacterials for the treatment of vaginitis caused by *Hemophilus vaginalis* or antifungals for the treatment of vulvovaginitis candidiasis caused by *Candida albicans* and related species.

Compressed Tablets

The physical features of compressed tablets are well known. Some are: round, oblong, or unique in shape; thick or thin; large or small in diameter; flat or convex; unscored or *scored* (Fig. 7.26) in halves, thirds, or quadrants; engraved or imprinted with an identifying symbol and/or code number; coated or uncoated; colored or uncolored; single layer, or bi- or tri-layered.

Tablet diameters and shapes are determined by the die and punches used in the compression of the tablet. The less concave the punches, the more flat the resulting tablets; conversely, the more concave the punches, the more convex the resulting tablets (Fig. 7.27). Punches having raised impressions will produce recessed impressions on the tablets; punches having recessed etchings will produce tablets having raised impression or monograms. Monograms may be placed on one or on both sides of a tablet, depending upon whether monogram-producing lower and/or upper punches are used.

Quality Standards and Compendial Requirements

In addition to the apparent features of tablets, pharmacists are aware that tablets must meet other physical specifications and quality standards. These include criteria for tablet weight, weight variation,

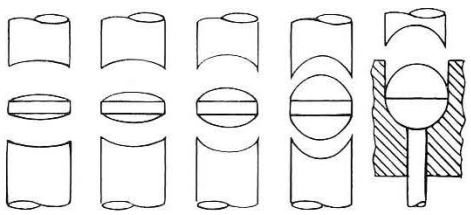

Fig. 7.27 *Contours of the punches determine the shape of the tablets. From left to right, flat face, shallow cup, standard cup, deep cup, and modified ball. (Courtesy of Cherry-Burrell Corporation.)*

content uniformity, tablet thickness, tablet hardness, tablet disintegration, and drug dissolution. These factors must be controlled during production (in-process controls) and verified after the production of each batch to assure that established product quality standards are met (Fig. 7.28).

TABLET WEIGHT AND USP WEIGHT VARIATION TEST. The quantity of fill placed in the die of a tablet press determines the weight of the resulting tablet. The volume of fill is adjusted with the first few tablets produced to yield tablets of the *desired weight and content.* For example, if a tablet is to contain 20 mg of a

Fig. 7.28 *Quality control in the manufacturing of tablets. (Courtesy of Eli Lilly and Company.)*

drug substance and if 100,000 tablets are to be produced, 2,000 g of drug are included in the formula. After the addition of the pharmaceutical additives such as the diluent, disintegrant, lubricant, and binder, the formulation may weigh 20 kg, which means that each tablet must weigh 200 mg for 20 mg of drug to be present. Thus, the depth of fill in the tablet die must be adjusted to hold a volume of granulation weighing 200 mg. During production, sample tablets are periodically removed for visual inspection and automated physical measurement (Fig. 7.29).

The USP contains a test for the determination of dosage-form uniformity by *weight variation* for uncoated tablets (14). In the test, 10 tablets are weighed individually and the average weight calculated. The tablets are assayed and the content of active ingredient in each of the 10 tablets is calculated assuming homogeneous drug distribution.

CONTENT UNIFORMITY. By the USP method, 10 dosage units are individually assayed for their content according to the assay method described in the individual monograph. Unless otherwise stated in the monograph, the requirements for content uniformity are met if the amount of active ingredient in each dosage unit lies within the range of 85% to 115% of the label claim and the relative standard deviation is less than 6.0%. If one or more dosage units does not meet these criteria, additional tests as prescribed in the USP are required (14).

TABLET THICKNESS. The thickness of a tablet is determined by the diameter of the die, the amount of fill permitted to enter the die, the compactability of the fill material, and the force or pressure applied during compression.

To produce tablets of uniform thickness during batch production and between batch productions for the same formulation, care must be exercised to employ the same factors of fill, die, and pressure. It should be pointed out that the degree of tableting pressure affects not only tablet thickness but also tablet hardness. And, tablet hardness is perhaps the more important criterion since it can affect tablet disintegration and drug dissolution. Thus, for tablets of uniform thickness and hardness, it is doubly important to control tableting pressure. Tablet thickness may be measured by hand gauge during production or by automated equipment. (Figs. 7.30, 7.31).

TABLET HARDNESS AND FRIABILITY. It is not unusual for a tablet press to exert as little as 3000 and as much as 40,000 pounds of force in the production of tablets. Generally, the greater the pressure applied, the harder the tablets, although the characteristics of the granulation also has a bearing on tablet hardness. Certain tablets, such as lozenges and buccal tablets that are intended to dissolve slowly, intentionally are made hard; other tablets, as those for immediate drug release are made soft. In general, tablets should be sufficiently

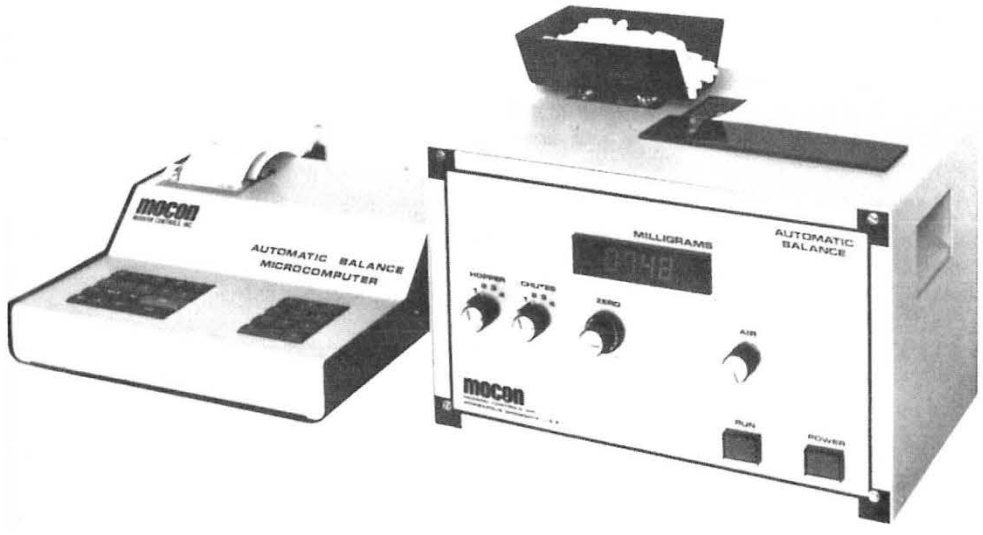

Fig. 7.29 *Automatic balance that weighs product and prints statistics to determine compliance with USP weight variation requirements for tablets. (Courtesy of Mocon Modern Controls, Inc.)*

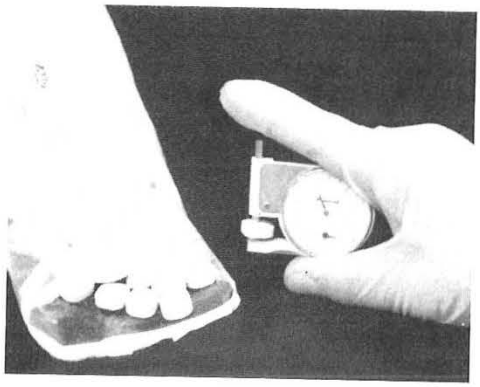

Fig. 7.30 *Tablet thickness gauge. (Courtesy of Eli Lilly and Company.)*

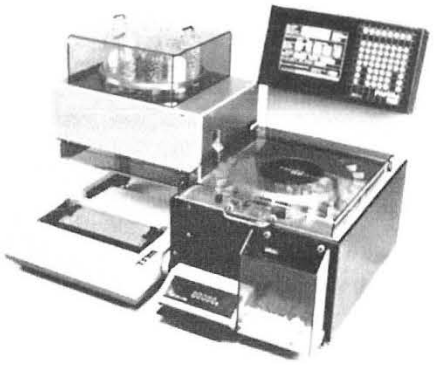

Fig. 7.31 *Automatic weight, hardness, thickness, and tablet diameter test instrument for quality control. Using a microprocessor and monitor for visualization, the instrument can test up to 20 samples at a time. (Courtesy of Scientific Instruments & Technology Corporation.)*

hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing.

Special dedicated hardness testers (Fig. 7.32) or multifunctional systems (Fig. 7.31) are used to measure the degree of force (in kilograms, pounds, or in arbitrary units) required to break a tablet. A force of about 4 kilograms is considered the minimum requirement for a satisfactory tablet. Multifunctional automated equipment can determine tablet weight, hardness, thickness and diameter.

A tablet's durability may be determined through the use of a *friabilator* (Fig.7.33). This apparatus determines the tablet's *friability,* or its tendency to crumble by allowing it to roll and fall within the rotating apparatus. The tablets are weighed before and after a specified number of rotations and any loss in weight determined. Resistance to loss of weight indicates the tablet's ability to withstand abrasion in handling, packaging, and shipment. A maximum weight loss of not more than 1% of the weight of the tablets being tested generally is considered acceptable for most products.

TABLET DISINTEGRATION. For the medicinal agent in a tablet to become fully available for absorption, the tablet must first disintegrate and discharge the drug to the body fluids for dissolution. Tablet disintegration also is important for those tablets containing medicinal agents (such as antacids and antidiarrheals) that are not intended to be absorbed but rather to act locally within the gastrointestinal tract. In these instances, tablet disintegration provides drug particles with an increased surface area for localized activity within the gastrointestinal tract.

All USP tablets must pass a test for disintegration, which is conducted *in vitro* using a testing apparatus as the one shown in Figure 7.34. The apparatus consists of a basket-rack assembly containing six open-ended transparent tubes of USP-specified dimensions, held vertically upon a 10-mesh stainless steel wire screen. During testing, a tablet is placed in each of the six tubes of the basket and through the use of a mechanical device, the basket is raised and lowered in the immersion fluid at a frequency of between 29 and 32 cycles per minute, the wire screen always being maintained below the level of the fluid. For uncoated tablets, buccal tablets, and sublingual tablets, water maintained at about 37°C serves as the immersion fluid unless another fluid is specified in the individual monograph. For

Fig. 7.32 *CompuTest hardness tester, tests in Newtons, Kilopond, and Strong Cobb. Automatic or manually operated. tests up to 100 tablets per run. Integrated software stores product test programs. (Courtesy of Vector Corporation).*

these tests, complete disintegration is defined as "that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core" (14).Tablets must disintegrate within the times set forth in the individual monograph, usually 30 minutes, but varying from about 2 minutes for Nitroglycerin Tablets to up to 4 hours for buccal tablets. If one or more tablets fail to disintegrate, additional tests prescribed by the USP must be performed.

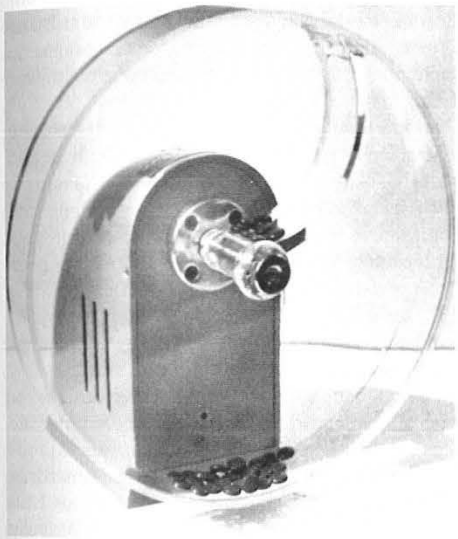

Fig. 7.33 *Erweka tablet testing apparatus for rolling and impact durability. Tablets are weighed and placed in the plexiglass drum in which a curved baffle is mounted. When the motor is activated by setting the timer, the tablets roll and drop. If the free fall within the drum results in the breakage or excessive abrasion of the tablets, they are considered not suited to withstand shipment without being damaged. The motor makes 20 rpm. After the tablets have been tested, they are removed and weighed again. The difference in weight within a given time indicates the rate of abrasion. (Courtesy of Chemical and Pharmaceutical Industry Co.)*

Enteric-coated tablets are similarly tested, except that the tablets are permitted to be tested in simulated gastric fluid for one hour after which no sign of disintegration, cracking, or softening must be seen. They are then actively immersed in the simulated intestinal fluid for the time stated in the individual monograph during which time the tablets disintegrate completely for a positive test.

TABLET DISSOLUTION. In vitro dissolution testing of solid dosage forms is important for a number of reasons (15).

1. It guides the formulation and product development process toward product optimization. By conducting dissolution studies in the early stages of a product's development, differentiations can be made between formulations and correlations identified with in vivo bioavailability data.
2. The performance of the manufacturing process may be monitored by dissolution testing, as a component of the overall quality assurance program. The conduct of such testing from the early product development through product approval and commercial batch production assures the control of any potential variables of materials and processes which could affect drug dissolution and the product's quality standards.
3. Consistent in vitro dissolution testing results assure bioequivalence from batch-to-batch. In assessing such batch-to-batch bioequivalence, the

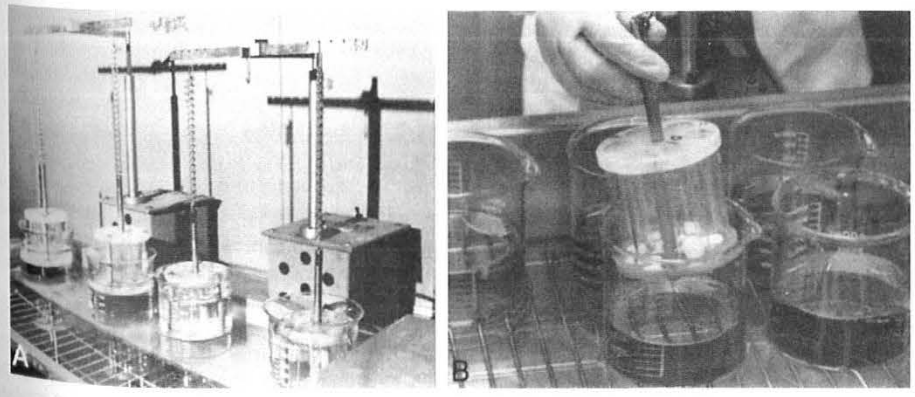

Fig. 7.34 *Tablet disintegration testing apparatus. (Courtesy of Eli Lilly and Company.)*

FDA allows manufacturers to examine scale-up batches of 10% of the proposed size of the actual production batch, or 100,000 dosage units, whichever is greater.

4. As a requirement for regulatory approval for product marketing for products registered with the FDA and regulatory agencies of other countries. New drug applications (NDAs) submitted to the FDA contain in vitro dissolution data generally obtained from batches that have been used in pivotal clinical and/or bioavailability studies and from human studies conducted during product development (16). Once the specifications are established in an approved NDA, they become official (USP) specifications for all subsequent batches and bioequivalent products.

The goal of in vitro dissolution testing is to provide insofar as is possible, a reasonable prediction of, or correlation with, the product's in vivo bioavailability. A system has been developed which relates combinations of a drug's solubility (high or low) and its intestinal permeability (high or low) as a possible basis for predicting the likelihood of achieving a successful in vivo-in vitro correlation (IVIVC) (16–17). Considered are drugs determined to have:

High Solubility and High Permeability
Low Solubility and High Permeability
High Solubility and Low Permeability
Low Solubility and Low Permeability

For a high solubility and high permeability drug, an IVIVC may be expected if the dissolution rate is slower than the rate of gastric emptying (the rate limiting factor) (18). In the case of a low solubility and high permeability drug, drug dissolution may be the rate limiting step for drug absorption and an IVIVC may be expected. In the case of a high solubility and low permeability drug, permeability is the rate-controlling step and only a limited IVIVC may be possible. In the case of a drug with low solubility and low permeability, significant problems would be likely for oral drug delivery (16).

As noted previously, tablet disintegration is the important first step to the dissolution of the drug substance contained in a tablet. A number of formulation and manufacturing factors can affect the disintegration and dissolution of a tablet including: the particle size of the drug substance in the formulation; the solubility and hygroscopicity of the formulation; the type and concentration of the disintegrant, binder, and lubricant used; the manufacturing method, particularly the compactness of the granulation and the compression force used in tableting; and the in-process variables which may occur (19). Together, these factors present a set of complex interrelated conditions which have a bearing on a product's dissolution characteristics. Therefore, it is vitally important for batch-to-batch consistency to establish dissolution test standards and controls for both materials and processes, and to implement them during production and in final testing.

In addition to formulation and manufacturing controls, the method of dissolution testing also must be controlled to minimize important variables, as paddle rotational speed, vibration, and disturbances by sampling probes. Dissolution testing for orally administered dosage forms has been a component of evaluating product quality in the USP since 1970 when only twelve monographs contained such a requirement. Today, the requirement is standard for tablets and capsules.

The USP includes seven apparatus designs for drug release and dissolution testing of immediate release oral dosage forms, extended release products, enteric coated products, and transdermal drug delivery devices. Of primary interest here are USP Apparatus 1 and USP Apparatus 2, used principally for immediate release solid oral dosage forms.

The equipment consist of 1) a variable speed stirrer motor, 2) a cylindrical stainless steel basket on a stirrer shaft (USP Apparatus 1) or a paddle as the stirring element (USP Apparatus 2), 3) a 1000-mL vessel of glass or other inert, transparent material, fitted with a cover having a center port for the shaft of the stirrer, and three additional ports, two for the removal of samples, and one for the placement of a thermometer, and 4) a suitable water bath to maintain the temperature of the dissolution medium in the vessel. In using USP Apparatus 1, the dosage unit is placed inside the basket. In using USP Apparatus 2, the dosage unit is placed in the vessel.

In each test, a volume of the dissolution medium (as stated in the individual monograph) is placed in the vessel and allowed to come to 37°C ± 0.5°C. Then, the stirrer is rotated at the speed specified and at stated intervals, samples of the medium are withdrawn for chemical analysis of the proportion of drug dissolved. The tablet or capsule must meet the stated monograph requirement for rate of dissolution. For example, "not less than 85% of the labeled amount is dissolved in 30 minutes."

There is growing recognition that where problems of inconsistencies in dissolution occur, they occur not between dosage units from the *same* production batch, but rather *between batches* or be-

tween products from different manufactures, most likely due to the many factors of formulation, materials, and manufacturing pointed out above. However, since dosage units within a batch are generally not the problem, the concept of "pooled dissolution testing" has emerged. This process recognizes the concept of "batch characteristics" and allows pooled specimens to be tested. The pooled specimens may be sampled from the individual dissolution vessels in the apparatus or from multiple dosage units dissolved in a single vessel (20).

Sophisticated and highly automated equipment is continually being developed to provide high levels of quality assurance and control to the dissolution test process (Figs. 7.35, 7.36).

Compressed Tablet Manufacture

Compressed tablets may be made by three basic methods: *wet granulation, dry granulation,* and *direct compression.* Figure 7.37 presents schematic drawings of each method.

Most powdered medicinal agents require the addition of excipients as diluents, binders, disintegrants, and lubricants to provide the desired characteristics for tablet manufacture and efficacious use. One important requirement in tablet manufacture is that the drug mixture is free-flowing from the hopper of the tablet press into the dies to enable the high-speed compression of the powder mix into tablets. Granulations of powders provide this free-flowing quality. Granulations also increase material density thereby improving powder compressibility during tableting.

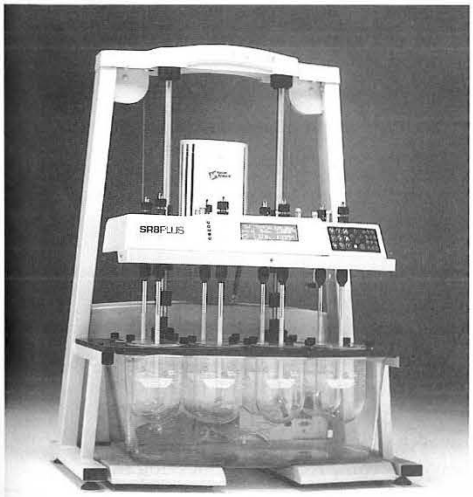

Fig. 7.35 *Hanson SR8-Plus Dissolution Test System. Features microprocessor and templates to create, edit, store, and validate dissolution protocols, graphical displays with menues and icon-based program controls. (Courtesy of Hanson Research Corporation).*

Wet Granulation

Wet granulation is a widely employed method for the production of compressed tablets. The steps required are: 1) weighing and blending the ingredients, 2) preparing a damp mass, 3) screening the damp mass into pellets or granules, 4) drying the granulation, 5) sizing the granulation by dry screening, 6) adding lubricant and blending, and 7) tableting by compression.

WEIGHING AND BLENDING. Specified quantities of active ingredient, diluent or filler, and disintegrating agent are mixed by mechanical powder blender or mixer until uniform.

Among the fillers used are lactose, microcrystalline cellulose, starch, powdered sucrose, and calcium phosphate. The choice of the filler usually is based on the experience of the manufacturer with the material, its relative cost, and its compatibility with the other formulation ingredients. For example, calcium salts must not be used as fillers with tetracycline antibiotics, because of an interaction between the two agents which results in reduced tetracycline absorption from the gastrointestinal tract. Among the fillers most preferred are lactose because of its solubility and compatibility, and microcrystalline cellulose, because of its compactability, compatibility, and the consistent uniformity of supply (21).

Disintegrating agents include croscarmellose, corn and potato starches, sodium starch glycolate, sodium carboxymethylcellulose, polyvinyl polypyrolidone (PVP), crospovidone, cation-exchange resins, alginic acid, and other materials that swell or expand on exposure to moisture and effect the rupture or breakup of the tablet in the gastrointestinal tract. Croscarmellose (2%) and sodium starch glycolate (5%) are often preferred because of their high water uptake and rapid action. One commercial brand of sodium starch glycolate is reported to swell up to 300% of its volume in water (22). When starch is employed, 5% to 10% is usually suitable but up to about 20% may be used to promote more rapid tablet disintegration. The total amount of disintegrant used is not always added in preparing the granulation. Often a portion (sometimes half) is reserved and added to the finished granulation

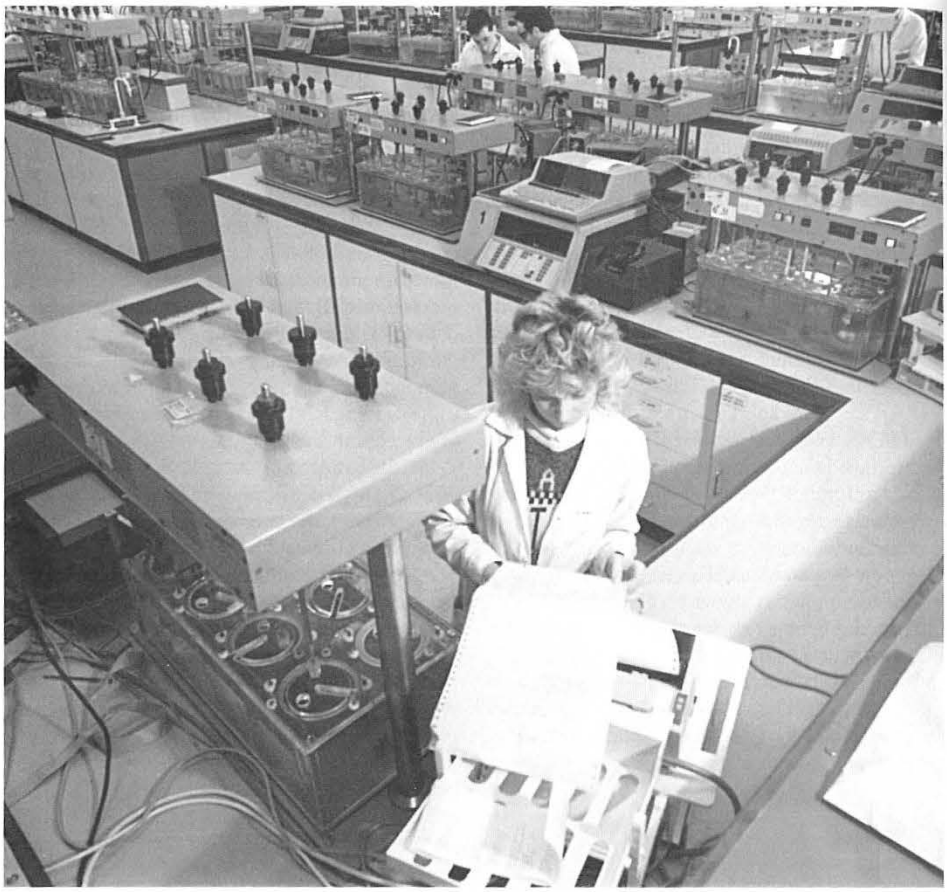

Fig. 7.36 *A modern computerized laboratory dedicated to studies of drug dissolution from solid dosage forms. Included are Erweka dissolution baths, Hewlett-Packard computers, and Hewlett-Packard diode assay spectrophotometers. (Courtesy of Elan Corporation, plc.)*

prior to tableting. This results in a double disintegration of the tablet. One portion assists in the break-up of the tablet into pieces and the other portion assists in the break-up of the pieces into fine particles.

PREPARING THE DAMP MASS. A liquid binder is added to the powder mixture to facilitate the adhesion of the powder particles. A damp mass resembling dough is formed and is used to prepare the granulation. A good binder results in appropriate tablet hardness and does not negatively impact on the release of the drug from the tablet.

Among the binding agents used are povidone, an aqueous preparation of corn starch (10–20%), glucose solution (25–50%), molasses, methylcellulose (3%), carboxymethylcellulose, and microcrystalline cellulose. If the drug substance is adversely affected by an aqueous binder, a nonaqueous solution, or a dry binder may be used. The amount of binding agent used is part of the operator's art; however, the resulting binder-powder mixture should be compactible by squeezing in the hand. The binding agent contributes to the adhesion of the granules to one another and maintains the integrity of the tablet after compression. However, care must be exercised not to over-wet or under-wet the powder. Over-wetting can result in granules that are too hard for proper tableting and under-wetting can result in tablets that are too soft and tend to crumble. When desired, a colorant or

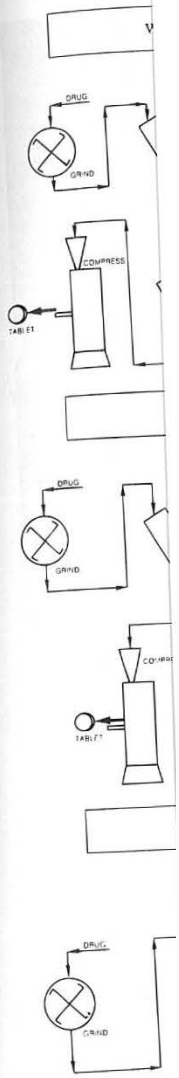

Fig. 7.37 *Schem*
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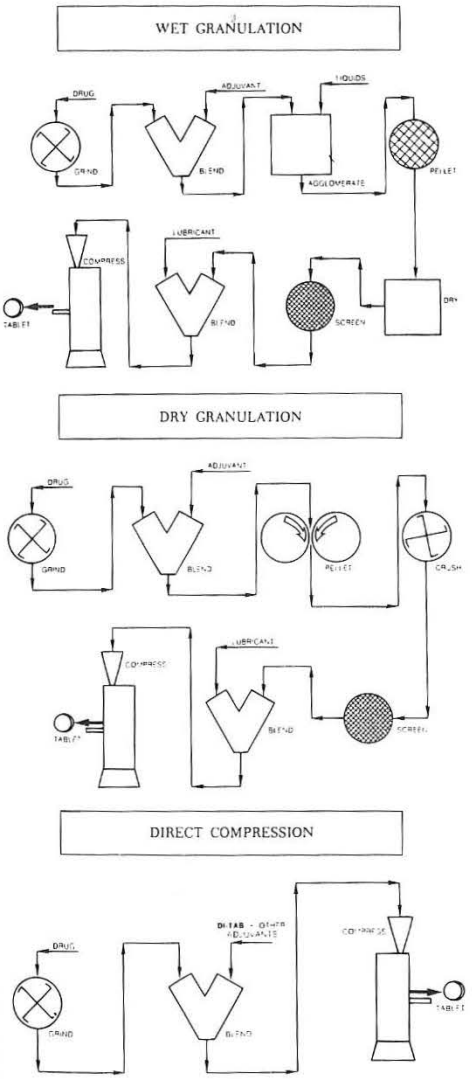

Fig. 7.37 *Schematic drawings of the three main methods for the preparation of tablets: wet granulation (top); dry granulation (center); direct compression (bottom). (Courtesy of Stauffer Chemical Co.)*

flavorant may be added to the binding agent to prepare a granulation having an added feature.

SCREENING THE DAMP MASS INTO PELLETS OR GRANULES. The wet mass is pressed through a screen (usually No. 6- or 8-mesh) to prepare the granules. This may be done by hand or by special equipment which prepares the granules by extrusion through perforations in the apparatus. The resultant granules are spread evenly on large pieces of paper in shallow trays and dried.

DRYING THE GRANULATION. Granules may be dried in thermostatically controlled ovens which constantly record the time, temperature, and humidity (Fig. 7.38).

SIZING THE GRANULATION BY DRY SCREENING. After drying, the granules are passed through a screen of a smaller mesh than that used to prepare the original granulation. The degree to which the granules are reduced depends upon the size of the punches to be used. In general, the smaller the tablet to be produced, the smaller are the granules used. Screens from 12- to 20-mesh size are generally used for this purpose. Sizing of the granules is necessary so that the die cavities for tablet compression may be completely and rapidly filled by the free-flowing granulation. Voids or air spaces left by too large a granulation would result in the production of uneven tablets.

ADDING LUBRICATION AND BLENDING. After dry screening, a dry lubricant is dusted over the spread-out granulation through a fine mesh screen. Lubricants contribute to the preparation of compressed tablets in several ways: they improve the flow of the granulation in the hopper to the die cavity; they prevent the adhesion of the tablet formulation to the punches and dies during compression; they reduce friction between the tablet and the die wall during the tablet's ejection from the tablet machine; and, they give a sheen to the finished tablet. Among the more commonly used lubricants are magnesium stearate, calcium stearate, stearic acid, talc, and sodium stearyl fumarate. Magnesium stearate is the most-used (21). The quantity of lubricant used varies from one tableting operation to another, but usually ranges from about 0.1% to 5% of the weight of the granulation.

All-In-One Granulation Methods

Technologic advances now allow the entire process of granulation to be completed in a continuous *fluid-bed process*, using a single piece of equipment, the fluid-bed granulator (Figs. 7.39, 7.40).

The fluid-bed granulator performs the following steps: 1) preblending the formulation powder, including active ingredients, fillers, disintegrants, in a bed by fluidized air, 2) granulating the mixture by spraying onto the fluidized powder bed, a suitable liquid binder, as an aqueous solution of acacia, hydroxypropyl cellulose, or povidone, and 3) drying the granulated product to the desired moisture content.

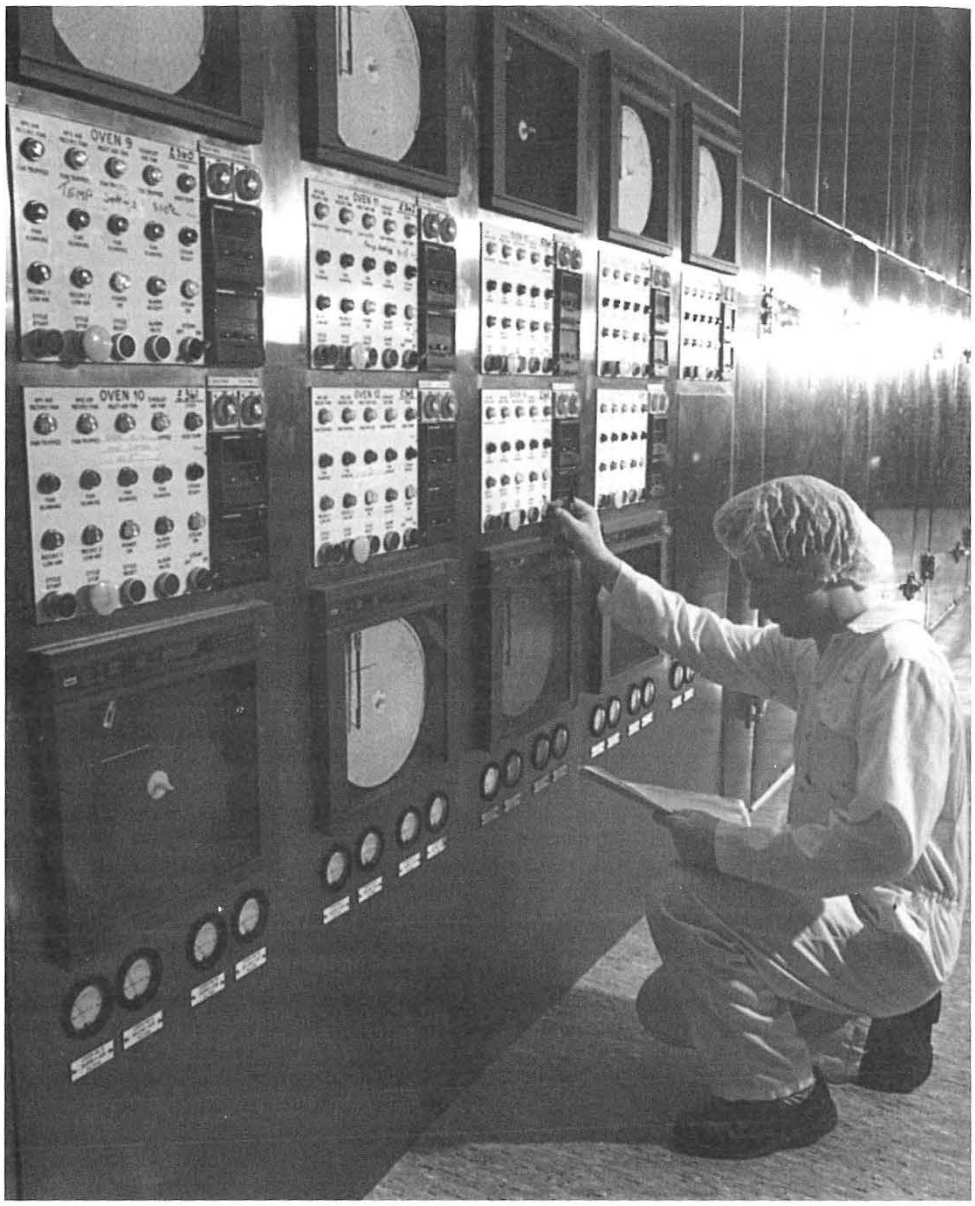

Fig. 7.38 *Temperature controlled Casburt Drying Oven used in the preparation of granules and controlled release beads. (Courtesy of Elan Corporation, plc.)*

Another method, the microwave vacuum processing method, also allows the powders to be tableted to be mixed, wetted, agglomerated, and dried within the confines of a single piece of equipment (Fig. 7.41). The wet mass is dried by gentle mixing, vacuum, and microwave. The use of the microwave for the drying process reduces the drying time considerably, often by one-fourth. The total-batch production time is usually in the range of 90 minutes. After adding lubricants and

Fig. 7.39 *Example of fluid bed granulator. (Courtesy of Schering Laboratories.)*

screening, the batch is ready for tableting or capsule filling.

Dry Granulation

By the dry granulation method, the powder mixture is compacted in large pieces and subsequently broken down or sized into granules (see Fig. 7.37). By this method, either the active ingredient or the diluent must have cohesive properties. Dry granulation is especially applicable to materials that cannot be prepared by wet granulation due to their degradation by moisture or by the elevated temperatures required for drying the granules.

SLUGGING. In this method, after weighing and mixing the ingredients, the powder mixture is "slugged" or compressed into large flat tablets or pellets of about 1 inch in diameter. The slugs then are broken up by hand or by a mill (Fig. 7.42) and passed through a screen of desired mesh for sizing. Lubricant is added in the usual manner, and tablets are prepared by compression. Aspirin, which is hydrolyzed on exposure to moisture, may be prepared into tablets after slugging.

ROLLER COMPACTION. Instead of slugging, powder compactors may be used to increase the density of a powder by pressing it between high-pressure rollers at 1 ton to 6 tons of pressure. The densified material then is broken up, sized, and lubricated, and tablets are prepared by compression in the usual manner. The *roller compaction* method is often preferred over slugging. Binding agents used in roller compaction formulations include methylcellulose or hydroxymethylcellulose (6 to 12%) and can produce good tablet hardness and friability (23).

Tableting of Granulation

There are a number of types of tablet presses or tableting machines, each varying in productivity but similar in basic function and operation. They all compress a tablet formulation within a steel die cavity by the pressure exerted by the movement of two steel punches, a lower punch and an upper punch (Fig 7.43).

The operation of a single-punch describes the basic mechanical process. As the lower punch drops, the feed shoe filled with granulation from the hopper is positioned over and fills the die cavity. The feed shoe retracts, scrapes away the excessive granulation, and levels the layer of fill in the die cavity. The upper punch lowers and compresses the fill, forming the tablet. The upper punch then retracts as the lower punch rises with the formed tablet to

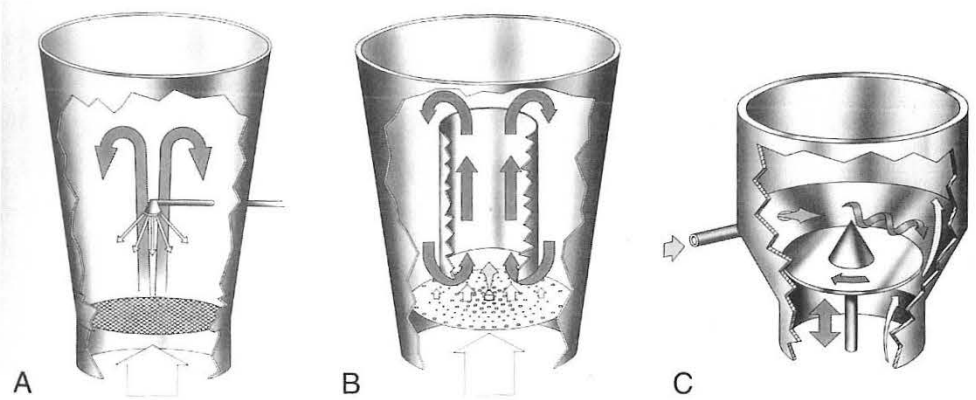

Fig. 7.40 *A, Top-spray; B, bottom-spray (Wurster); and C, tangential-spray methods in the fluid-bed coating of solid particles. (Courtesy of Glatt Air Techniques, Inc.)*

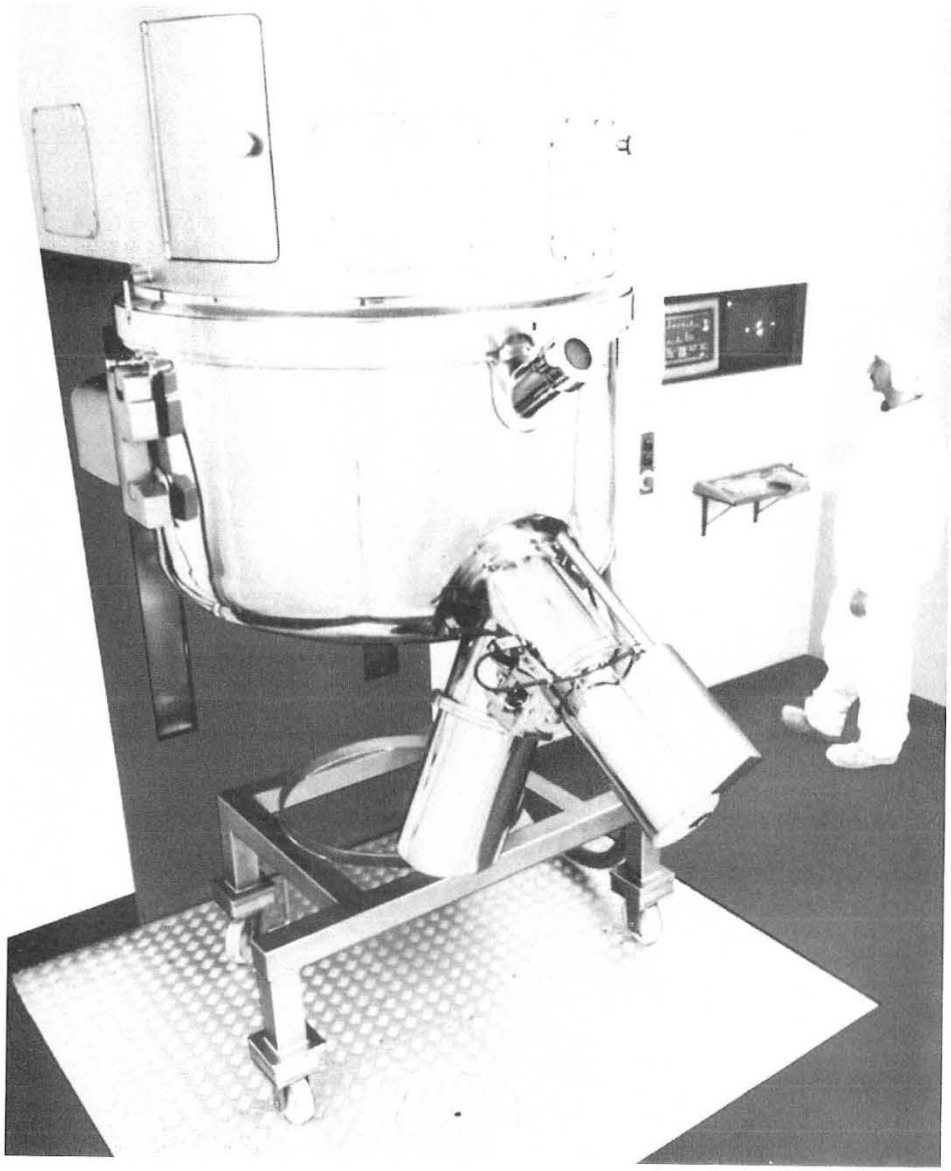

Fig. 7.41 *Microwave vacuum processing in which tableting ingredients are dry mixed, wetted with a binding liquid, and dried by vacuum and microwave within a single piece of equipment. (Courtesy of GEI Processing, Inc.)*

the precise level of the stage. The feed shoe moves over the die cavity, shoves the tablet aside, and once again fills the cavity with granulation to repeat the process. The tablets fall into a collection container. Samples of tablets are assayed/tested for the various quality standards described earlier.

Rotary tablet machines equipped with multiple punches and dies operate through the continuous rotating movement of the punches A single rotary press with 16 stations (16 sets of punches and dies) may produce up to 1150 tablets per minute. Double rotary tablet presses with 27, 33, 37, 41, or 49

Fig. 7.42 *Frewitt Oscillator or Fitz Mill utilized in the pulverization or granulation process. (Courtesy of Eli Lilly and Company.)*

sets of punches and dies are capable of producing 2 tablets for each die. Some of these machines can produce 10,000 and more tablets per minute of operation (Fig. 7.44). For such high speed production, induced die feeders are required to force fill material into the dies to keep up with the rapidly moving punches (Fig. 7.45). A consequence of high-speed production is the increased occurrence of *lamination* (horizontal striations) and tablet *capping,* in which the top of the tablet separates from the whole because the fill material does not have enough time to bond after compression. Reduced tableting speed remedies the problem (24).

Multiple-layered tablets are produced by the multiple feed and multiple compression of fill material within a single die. Tablets having an inner core

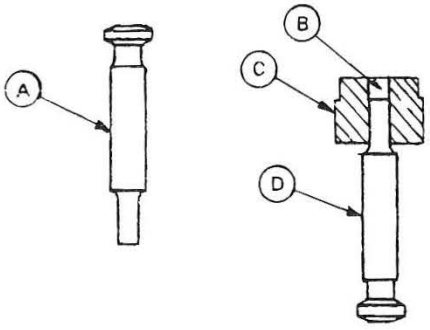

Fig. 7.43 *Punch and die set: A, upper punch; B, die cavity; C, die; and D, lower punch. (Courtesy of Cherry-Burrell Corporation.)*

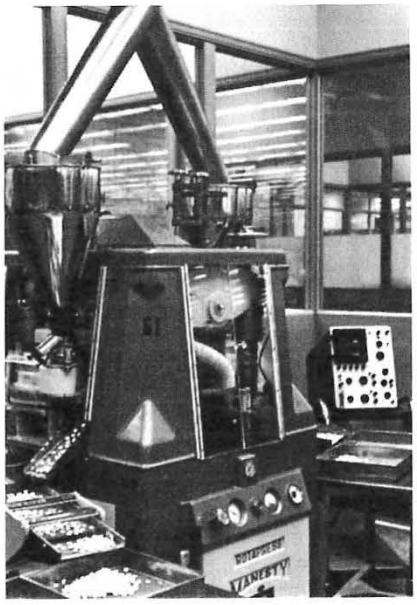

Fig. 7.44 *Manesty Rotapress rotary compression machine making compressed tablets. Tablets leaving the machine run over a tablet duster to screen where they are inspected. Material to be compressed is being fed from overhead hopper through yoke to each of the two compressing machine hoppers. Hardness of tablet is monitored electronically by oscilloscope at the right. (Courtesy of The Upjohn Company.)*

tablet are prepared by machines having a special feed apparatus which strategically places the core tablet within the die for compression with surrounding fill.

Direct Compression Tableting

Some granular chemicals, like potassium chloride, possess free flowing and cohesive properties that enable them to be compressed directly in a tablet machine without need of wet or dry granulation. For chemicals that do not possess this quality, special pharmaceutical excipients may be used which impart the necessary qualities for the production of tablets by direct compression. These tableting excipients include: *fillers,* as spray-dried lactose, microcrystals of alpha-monohydrate lactose, sucrose-invert sugar-corn starch mixtures, microcrystalline cellulose, crystalline maltose, and dicalcium phosphate; *disintegrating agents,* as direct-compression starch, sodium carboxymethyl starch, cross-linked carboxymethylcellulose fibers, and cross-linked polyvinylpyrrolidone; *lubricants,* as magnesium stearate and talc; and *glidants,* as fumed silicon dioxide.

The capping, splitting, or laminating of tablets is sometimes related to air entrapment during direct compression. When air is entrapped, the resulting tablets expand when the pressure of tableting is released, resulting in splits or layers in the tablets. Forced or induced feeders can reduce air entrapment, making the fill powder more dense and amenable to compaction.

Capping also may be caused by punches that are not immaculately clean and perfectly smooth or by a granulation which has too great a proportion of "fines" or fine powder. Fine powder, which results when a dried granulation is sized, is generally 10 to

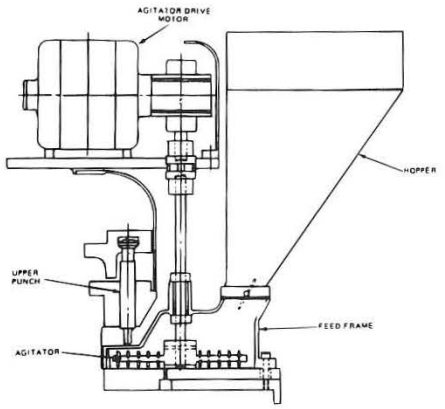

Fig. 7.45 *Induced die feeder. The standard gravity-fed open feed frame can be replaced with an induced die feeder. Using this accessory, granulation is forced into the die by the rotary action of the agitator. (Courtesy of Cherry-Burrell Corporation.)*

20% of the weight of the granulation. Some fine powder is desired to properly fill the die cavity. However, an excess can also lead to tablet softness and capping.

Tablets that have aged or which have been stored improperly also may exhibit splitting or other physical deformations (Fig. 7.46).

Tablet Dedusting

To remove traces of loose powder adhering to tablets following compression, the tablets are conveyed directly from the tableting machine to a tablet deduster. An example of this type of apparatus is shown in Figure 7.47. The compressed tablets may then be coated.

Chewable Tablets

Chewable tablets are pleasant tasting tablets formulated to disintegrate smoothly in the mouth with or without active chewing. They are prepared by wet granulation and compression, using only minimal degrees of tableting pressure in order to produce a soft tablet.

Mannitol, a white crystalline hexahydric alcohol, is used as the excipient in most chewable tablets. Mannitol is about 70% as sweet as sucrose with a cool feel in the mouth resulting from its negative heat of solution. In many chewable tablet formulations, mannitol may account for 50% or more of the weight of the formulation. Sometimes, other sweetening agents, as sorbitol, lactose, dextrose, crystalline maltose, and glucose, may be substituted for part or all of the mannitol. In the preparation of sugar-free chewable tablets, xylitol may be used. Xylitol is sweeter than mannitol and has the desirable negative heat of solution that provides the cool mouth feel upon dissolution.

Lubricants and binders that do not detract from the texture or desired hardness of the tablet may be used. To enhance the appeal of the tablets, colorants and tart or fruity flavorants are commonly employed. Among the types of products prepared as chewable tablets are antacids (e.g., calcium carbonate), antibiotics (e.g., erythromycin), anti-infective agents (e.g., didanosine), anticonvulsants (e.g.,carbamazepine), vasodilators (e.g., isosorbide dinitrate), analgesics (e.g., acetaminophen), various vitamins and cold/allergy combination tablets. Chewable tablets are particularly useful for children and adults who have difficulty swallowing other solid dosage forms.

The following is a formula for a typical chewable antacid tablet:(25)

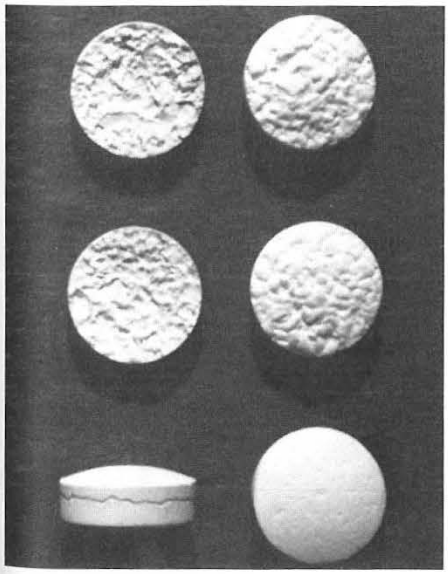

Fig. 7.46 *Tablets that have split on aging, due to conditions of manufacture or storage.*

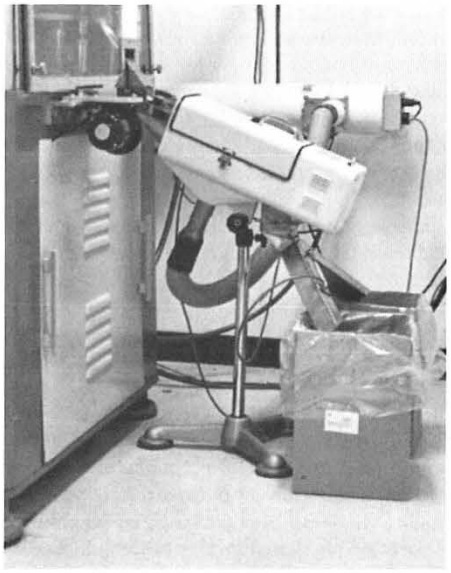

Fig. 7.47 *Model 25 Manesty Tablet Deduster. Tablets leaving tableting machine are dedusted and passed into collection containers. (Courtesy of Eli Lilly and Company.)*

Per Tablet	
Aluminum hydroxide,	325.0 mg
Mannitol,	812.0 mg
Sodium saccharin,	0.4 mg
Sorbitol (10% w/v solution),	32.5 mg
Magnesium stearate,	35.0 mg
Mint flavor concentrate,	4.0 mg

Preparation: Blend the aluminum hydroxide, mannitol, and sodium saccharin. Prepare a wet granulation with the sorbitol solution. Dry at 120°F and screen through a 12-mesh screen. Add the flavor and magnesium stearate, blend, and compress into tablets.

Molded Tablets

The commercial preparation of tablets by molding has been replaced by the tablet compression process. However, molded tablets, or *tablet triturates,* may be prepared on a small laboratory scale as follows.

The mold used in the preparation of molded tablets is made of hard rubber, hard plastic, or metal. It has two parts, the upper part, or *die* portion, and the lower part containing squat, flat *punches.* The die portion is a flat plate the thickness of the tablets to be produced and has 50 to 200 uniformly drilled and evenly spaced circular holes (Fig. 7.48). The lower part of the mold has corresponding punches that fit the holes precisely. When the die is filled with tableting material and placed atop the punches, the punches gently lift the fill material from the holes to rest upon the punches for drying.

The base for molded tablets is generally a mixture of finely powdered lactose with or without a portion of powdered sucrose (5–20%). The addition of sucrose results in less-brittle tablets. In preparing the fill, the drug is mixed uniformly with the base, by geometric dilution when potent drugs are used. The powder mixture is wetted with a 50% mixture of water and alcohol sufficient only to dampen the powder so that is may be compacted. The solvent action of the water on a portion of the lactose/sucrose base effects the binding of the powder mixture upon drying. The alcohol portion hastens the drying process.

The upper mold is placed on a clean flat glass surface and the damp mass added by a rubbing motion. When each opening is filled completely, top and bottom, the mold is fitted on the punch portion of the mold and the tablets raised to dry.

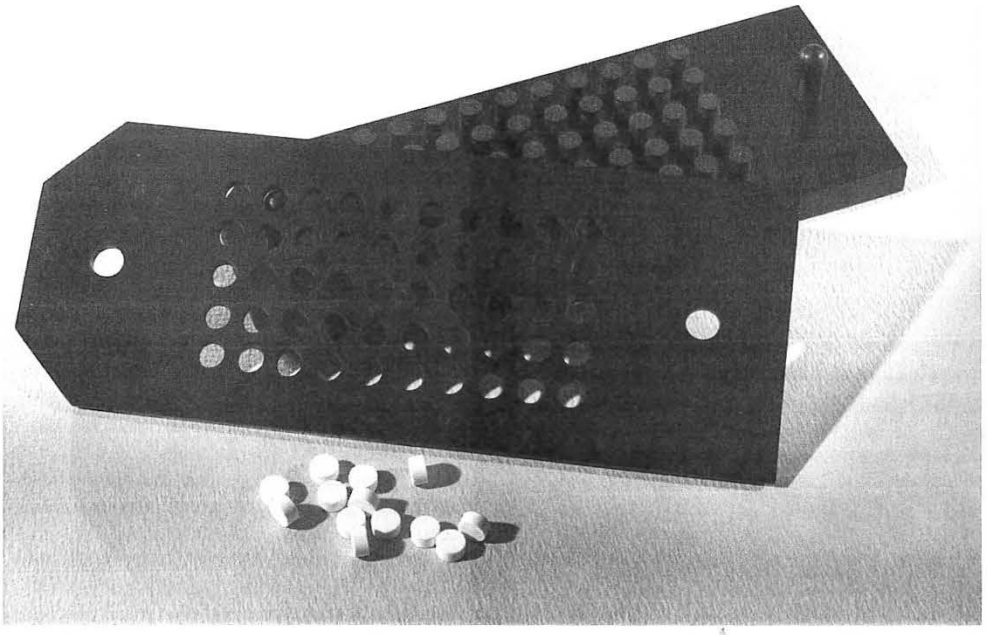

Fig. 7.48 *Laboratory tablet mold for the preparation of tablet triturates.*

Before use, the mold should be "standardized" for the fill material used, since the densities of different formulas result in tablets of different weights. This may be done by preparing a test batch of the formula and weighing and recording the weight of the dry tablets produced. This weight is then used in calculations for production quantities.

Molded tablets are intended to dissolve rapidly in the oral cavity. They do not contain disintegrants, lubricants, or coatings to slow their rate of dissolution.

AUTHORS' NOTE: *A more complete discussion of the preparation of molded tablets and the standardization of laboratory molds may be found in the 5th edition of this textbook.*

Tablet Coating

Tablets are coated for a number of reasons, including to: protect the medicinal agent against destructive exposure to air and/or humidity; mask the taste of the drug; provide special characteristics of drug release (e.g., enteric coatings); and to provide aesthetics or distinction to the product.

In a limited number of instances, tablets are coated to prevent inadvertent contact by nonpatients with the drug substance and the consequent effects of drug absorption. For example, Proscar tablets (finasteride, Merck) are coated for just this reason. The drug is used by men in the treatment of benign prostatic hyperplasia. The labeling instructions warn that women who are pregnant or who could become pregnant should not come into contact with the drug. Drug contact can occur through the handling of broken tablets. If finasteride is absorbed by a woman who is pregnant with a male baby, the drug has the potential capacity to adversely affect the developing male fetus.

The general methods involved in coating tablets are as follows.

Sugarcoating Tablets

The sugarcoating of tablets may be divided into the following steps: 1) waterproofing and sealing (if needed), 2) subcoating, 3) smoothing and final rounding, 4) finishing and coloring (if desired), and 5) polishing. The entire coating process is conducted in a series of mechanically operated acorn-shaped coating pans of galvanized iron, stainless steel, or copper. The pans are partially open in the front, have diameters ranging from about 1 to 4 feet, and are of various capacities (Figs. 7.49, 7.50). The smaller pans are used for experimental, devel-

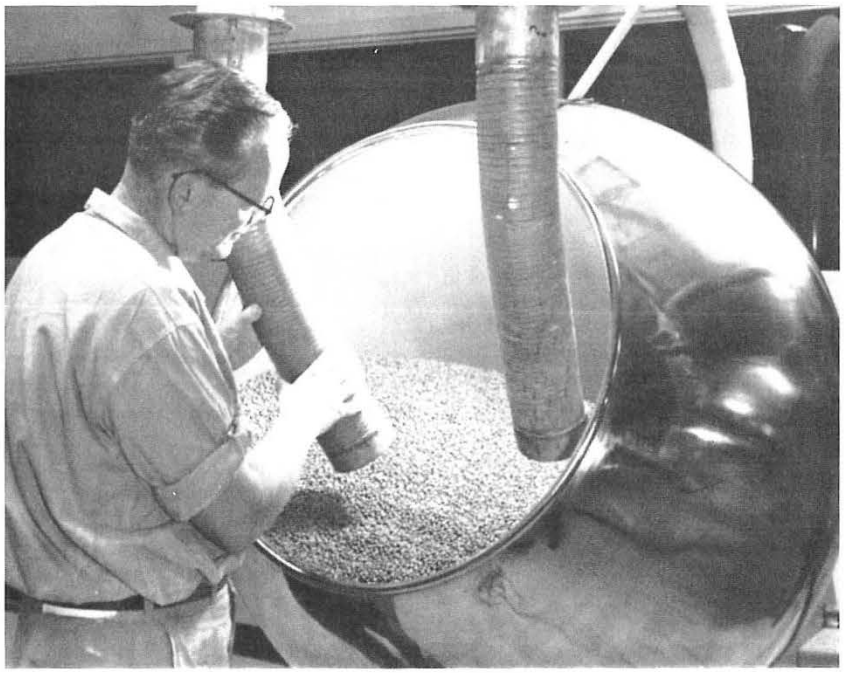

Fig. 7.49 *Tablet coating, an older style coating pan, showing the warm air supply and the exhaust. (Courtesy of Wyeth Laboratories.)*

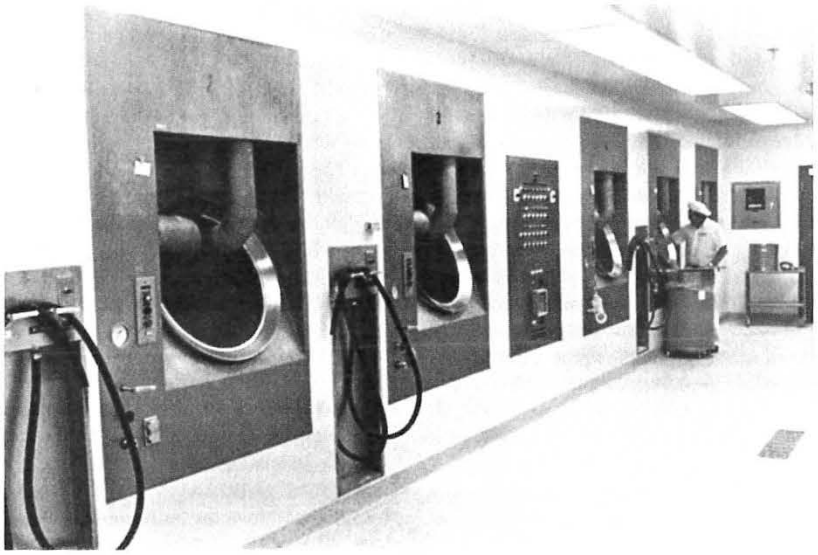

Fig. 7.50 *Modern tablet coating facility. Air and exhaust ducts to assist drying are automatically operated from central board. (Courtesy of Eli Lilly and Company.)*

opmental, and pilot plant operations, the larger pans for industrial production. The pans operate at about a 40° angle to contain the tablets while allowing the operator visual and manual access. During operation, the pan is mechanically rotated at moderate speeds, allowing the tablets to tumble over each other while making contact with the coating solutions which are gently poured or sprayed onto the tablets. To allow gradual build-up of the coatings, the solutions are added in portions, with warm air blown in to hasten drying. Each coat applied only after the previous coat has dried. Tablets intended to be coated are manufactured to be thin-edged and highly convex to allow the coatings to form rounded rather than angular edges.

WATERPROOFING AND SEALING COATS. For tablets containing components that may be adversely affected by moisture, one or more coats of a waterproofing substance, as pharmaceutical shellac or a polymer, is applied to the compressed tablets before the subcoating application. The waterproofing solution (usually alcoholic) is gently poured or sprayed on the compressed tablets rotating in the coating pans. Warm air is blown into the pan during the coating to hasten the drying and to prevent tablets from sticking together.

SUBCOATING. After the tablets are waterproofed (if needed), 3 to 5 subcoats of a sugar-based syrup are applied. This bonds the sugar coating to the tablet and provides rounding. The sucrose and water syrup also contains gelatin, acacia, or polyvinylpyrrolidone (PVP) to enhance the coating of the tablets. When the tablets are partially dry they are sprinkled with a dusting powder, usually a mixture of powdered sugar and starch but sometimes talc, acacia, or precipitated chalk as well. Warm air is applied to the rolling tablets, and when they are dry, the subcoating process is repeated until the tablets are of the desired shape and size (Fig. 7.51). The subcoated tablets are then scooped out of the coating pan and the excess powder is removed by gently shaking the tablets on a cloth screen.

SMOOTHING AND FINAL ROUNDING. After the tablets have been subcoated, 5 to 10 additional coatings of a thick syrup are applied to complete the rounding and smooth the coatings. This syrup is sucrose-based with or without additional components as starch and calcium carbonate. As the syrup is applied, the operator moves his hand through the rolling tablets to distribute the syrup and to prevent the tablets from sticking to one another. A dusting powder is often used between syrup applications. Warm air is applied to hasten the drying time of each coat.

FINISHING AND COLORING. To attain final smoothness and the appropriate color to the tablets,

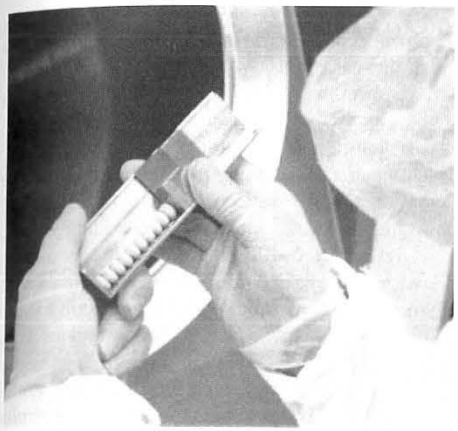

Fig. 7.51 *Tablet gauge used to measure the size of coated tablets. (Courtesy of Eli Lilly and Company.)*

several coats of a thin syrup containing the desired colorant are applied in the usual manner. This step is performed in a clean pan, free from previous coating materials.

IMPRINTING. Solid dosage forms may be passed through special imprinting machines (Fig. 7.52) to impart identification codes and other distinctive symbols. By FDA regulation, effective in 1995, all solid dosage forms for human consumption, including both prescription-only and over-the-counter drug products, must be imprinted with product-specific identification codes. Some exemptions to this requirement are allowed, namely: solid dosage forms used in clinical investigations; solid dosage forms that are extemporaneously compounded in the course of pharmacy practice; radiopharmaceutical drug products; and products that, because of their size, shape, texture or other physical characteristics, make imprinting technologically not feasible.

Technically, the imprint may be *debossed, embossed, engraved,* or printed on the surface with ink. *Debossed* means imprinted with a mark below the dosage form surface; *embossed* means imprinted with a mark raised above the dosage form surface; and *engraved* means imprinted with a code that is cut into the dosage form surface during production.

POLISHING. Coated tablets may be polished in several ways. Special drum-shaped pans or ordinary coating pans lined with fabric or canvas cloth impregnated with carnauba wax and/or beeswax, may be used to polish tablets as they tumble in the pan. Or, pieces of wax may be placed in a polishing pan and the tablets allowed to tumble over the wax until the desired sheen is attained. A third method involves the light-spraying of the tablets with wax dissolved in a nonaqueous solvent. Two or three coats of wax may be applied depending upon the desired gloss. After each coat has been applied, the addition of a small amount of talc to the tumbling tablets contributes to their high luster (Fig. 7.53).

Film-Coating Tablets

The sugarcoating process, as described, is not only tedious, time-consuming, and specialized, requiring the expertise of highly skilled technicians, but it also results in coated tablets that may be twice the size and weight of the original uncoated tablets. Also, sugar coated tablets may vary slightly in size from batch to batch and within a batch. All of these factors are important considerations for a manufacturer. From a patient's point of view, large

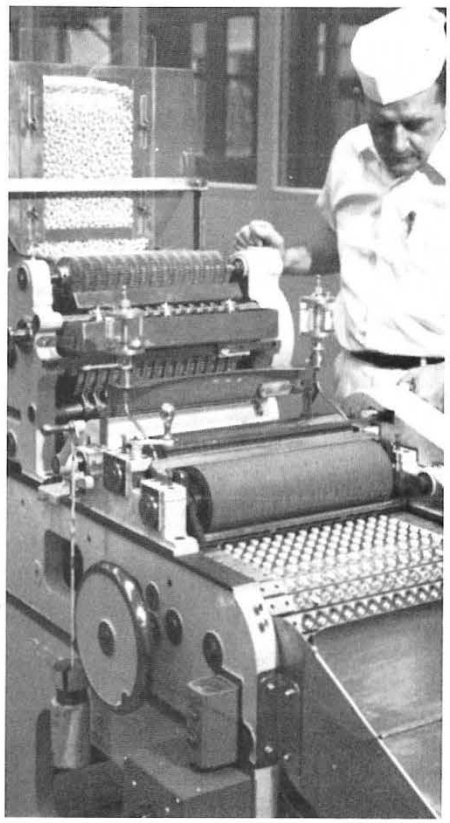

Fig. 7.52 *Branding of coated compression tablets on a Hartnett branding machine. (Courtesy of The Upjohn Company.)*

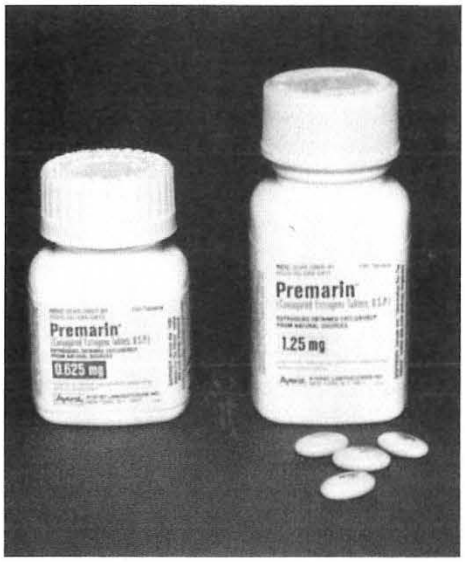

Fig. 7.53 *Example of coated, polished, and monogrammed tablets. (Courtesy of Wyeth-Ayerst Laboratories.)*

tablets are not as easily swallowed as are small tablets.

The film-coating process, which places a thin, skin-tight coating of a plastic-like material over the compressed tablet, was developed to produce coated tablets having essentially the same weight, shape, and size as the originally compressed tablet. And, the coating is thin enough to reveal any identifying monograms embossed in the tablet during its compression by the tablet punches. Film-coated tablets also are far more resistant to destruction by abrasion than are sugar-coated tablets. However, like sugar-coated tablets, the coating may be colored to make the tablets attractive and distinctive.

Film-coating solutions may be nonaqueous or aqueous. The nonaqueous solutions contain the following types of materials to provide the desired coating to the tablets:

1. A *film former* capable of producing smooth, thin films reproducible under conventional coating conditions and applicable to a variety of tablet shapes. Example: cellulose acetate phthalate.
2. An *alloying substance* providing water solubility or permeability to the film to ensure penetration by body fluids and therapeutic availability of the drug. Example: polyethylene glycol.
3. A *plasticizer* to produce flexibility and elasticity of the coating and thus provide durability. Example: castor oil.
4. A *surfactant* to enhance spreadability of the film during application. Example: polyoxyethylene sorbitan derivatives.
5. *Opaquants* and *colorants* to make the appearance of the coated tablets handsome and distinctive. Examples: Opaquant, titanium dioxide; colorant, FD&C or D&C dyes.
6. *Sweeteners, flavors,* and *aromas* to enhance the acceptability of the tablet to the patient. Examples: sweeteners, saccharin; flavors and aromas, vanillin.
7. A *glossant* to provide luster to the tablets without a separate polishing operation. Example: beeswax.
8. A *volatile solvent* to allow the spread of the other components over the tablets while allowing rapid evaporation to permit an effective yet speedy operation. Example: alcohol-acetone mixture.

Tablets are film coated by the application or spraying of the film-coating solution on the tablets in ordinary coating pans. The volatility of the solvent enables the film to adhere quickly to the surface of the tablets.

Due to both the expense of the volatile solvents used in the film-coating process and the environmental problem of the release of solvents, pharmaceutical manufacturers generally favor the use of aqueous-based film-coating solutions. One of the problems attendant to these, however, is the slow evaporation of the water-base compared to the volatile organic solvent-based solutions. One commercially available water-based colloidal coating dispersion is called AQUACOAT (FMC Corporation) and contains a 30% ethyl cellulose pseudolatex. Pseudolatex dispersions have a high solids content for greater coating ability and a relatively low viscosity. The low viscosity allows less water to be used in the coating dispersion, resulting in a lesser requirement for water-evaporation and a reduced likelihood of water interference with the tablet formulation. In addition, the low viscosity permits greater coat penetration into the crevices of monogrammed or scored tablets. A plasticizer may be incorporated into the dispersion to assist in the production of a denser, less-permeable film, with higher gloss and greater mechanical strength. Other aqueous film-coating products use cellulosic materials as methylcellulose, hydroxypropyl cellulose, and hydroxypropyl methylcellulose as the film forming polymer.

A typical aqueous film-coating formulation contains the following:(26)

1. *Film-forming polymer* (7–18%). Examples: cellulose ether polymers as hydroxypropyl methylcellulose, hydroxypropyl cellulose, and methylcellulose.
2. *Plasticizer* (0.5–2.0%). Examples: glycerin, propylene glycol, polyethylene glycol, diethyl phthalate, and dibutyl subacetate.
3. *Colorant and opacifier* (2.5–8%). Examples: FD&C or D&C Lakes and iron oxide pigments.
4. *Vehicle* (water, to make 100%).

There are some problems attendant to aqueous film-coating, including: the appearance of small amounts (*picking*) or larger amounts (*peeling*) of film fragments flaking from the tablet surface; roughness of the tablet surface due to failure of spray droplets to coalesce (*orange peel effect*); an uneven distribution of color on the tablet surface (*mottling*); filling-in of the score-line or indented logo on the tablet by the film (*bridging*); and the disfiguration of the core tablet when subjected for too long a period of time to the coating solution (tablet *erosion*). The cause of each of these problems can be determined and rectified through appropriate changes in formulation, equipment, technique or process (26).

Enteric Coating

Enteric coated solid dosage forms are intended to pass through the stomach intact to disintegrate and release their drug-content for absorption along the intestines. The design of an enteric coating may be based upon the transit time required for the passage of the dosage form from the stomach to the intestines and may be accomplished through coatings of sufficient thickness. However, usually an enteric coating is based upon factors of pH, resisting dissolution in the highly acid environment of the stomach but yielding to the less acid environment of the intestine. Some enteric coatings are designed to dissolve at pH 4.8 and greater.

Enteric coating materials may be applied to either whole compressed tablets or to drug particles or granules used in the subsequent fabrication of tablets or capsules. The coatings may be applied in multiple portions to build a thick coating or they may be applied as a thin film coat. The coating systems may be aqueous-based or organic-solvent-based and are effective so long as the coating material resists breakdown in the gastric fluid. Among the materials used in enteric coatings are pharmaceutical shellac, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, diethyl phthalate, and cellulose acetate phthalate.

Fluid-Bed or Air Suspension Coating

This process, using equipment of the type shown in Figure 7.54 involves the spray coating of powders, granules, beads, pellets or tablets held in suspension by a column of air. Fluid bed processing equipment is multifunctional and, as described

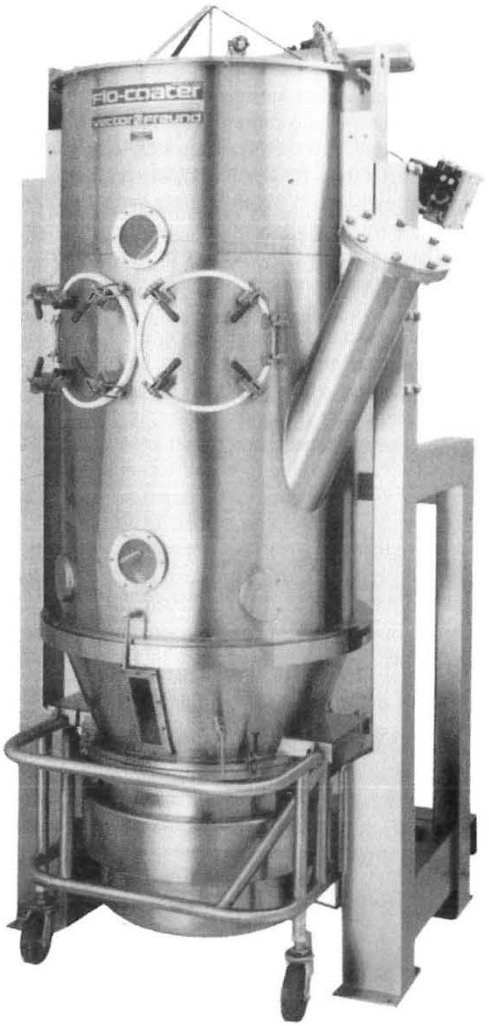

Fig. 7.54 *Vector/Freund Flo-Coater production system. A fluid bed system used in the application of coatings to beads, granules, powders, and tablets. Capacity of models ranges from 5 kg to 700 kg. (Courtesy of Vector Corporation.)*

previously, also may be used in preparing tablet granulations.

In the Wurster process, named after its developer, the items to be coated are fed into a vertical cylinder and are supported by a column of air that enters from the bottom of the cylinder. Within the air stream, the solids rotate both vertically and horizontally. As the coating solution enters the system from the bottom, it is rapidly placed on the suspended, rotating solids, with rounding coats being applied in less than an hour with the assistance of warm air blasts released in the chamber.

In another type of fluidized bed system, the coating solution is sprayed downward onto the particles to be coated as they are suspended by air from below. This method is commonly referred to as the *top-spray* method. This method provided greater capacity, up to 1500 kg, than do the other air suspension coating methods.(27) Both the top-spray and bottom-spray methods may be employed using a modified apparatus used for fluidized bed granulation. A third method, the *tangential-spray technique,* is used in rotary fluid-bed coaters. The bottom-, top-, and tangential-spray methods are depicted in Figure 7.40. Electron microscope images of the results of this process are shown in Fig. 7.55.

The three systems are increasingly used for the application of aqueous- or organic-solvent-based polymers as film coatings. The top-spray coating method is particularly recommended for taste masking, enteric release, and barrier films on particles or tablets. The method is most effective when coatings are applied from aqueous solutions, latexes, or hotmelts (27–28). The bottom-spray coating method is recommended for sustained-release and enteric-release products; and the tangential method for layering coatings, and for sustained-release and enteric-coated products (28).

Among the variables requiring control in order to produce product of desired and consistent quality are: equipment used and the method of spraying (e.g., top, bottom, tangential), spray-nozzle distance from spraying bed, spray (droplet) size, spray rate, spray pressure, volume of fluidization air, batch size, method(s) and time for drying, air temperature and moisture content in processing compartment (28).

Compression Coating

In a manner similar to the preparation of multiple compressed tablets having an inner core and an outer shell of drug material, core tablets may be sugarcoated by compression. The coating material, in the form of a granulation or powder, is compressed onto a tablet core of drug with a special tablet press. Compression coating is an anhydrous operation and thus may be safely employed in the coating of tablets containing a drug that is labile to moisture. Compared to sugarcoating using pans, compression coating is more uniform and uses less coating materials, resulting in tablets that are lighter, smaller, easier to swallow, and less expensive to package and ship.

Irrespective of the method used in coating, all tablets are visually or electronically inspected for physical imperfections (Fig. 7.56).

Impact of Manufacturing Changes on Solid Dosage Forms

The quality and performance of a solid dosage form may be altered by changes in formulation or by changes in the method of manufacture.

The changes in formulation could involve: 1) the

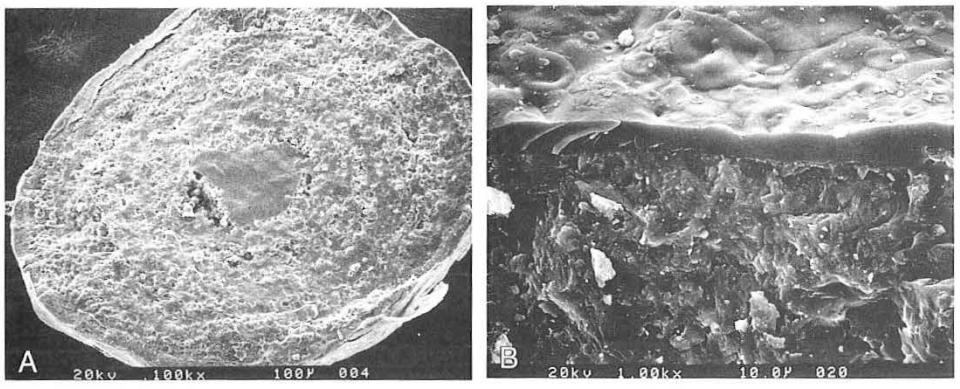

Fig. 7.55 *Scanning electron microscope images of pharmaceutical granules coated through fluid-bed technology: A, layered and coated granule; B, cross-section of top spray enteric coated granule. (Courtesy of Glatt Air Techniques, Inc.)*

Fig. 7.56 *Chec*
tablets. (Courtesy

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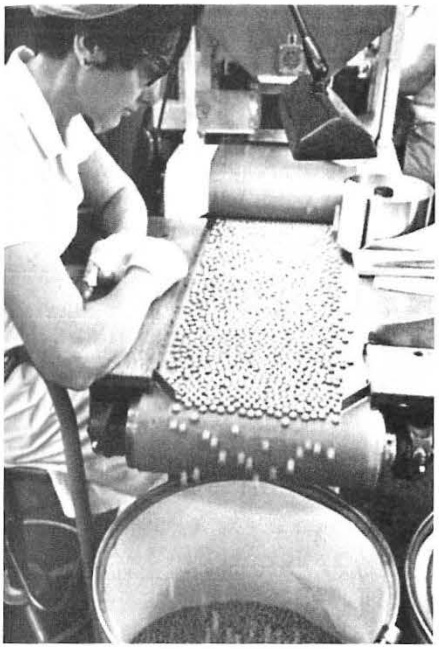

Fig. 7.56 *Checking for physical imperfections in coated tablets. (Courtesy of Smith, Kline & French.)*

use of starting raw materials, including both the active ingredient and pharmaceutical excipients, that have different chemical or physical characteristics (as solubility or particle size) than the standards set for the original components; 2) the use of different pharmaceutical excipients (e.g., magnesium stearate instead of calcium stearate as the lubricant); 3) the use of different quantities of the same excipients in a formulation (e.g., use of a more concentrated wet tablet binder); or 4) the addition of a new excipient to a formulation (as a revised tablet coating formula.

The changes in the method of manufacture could involve: 1) use of processing or manufacturing equipment or a different design; 2) a change in the steps or order in the process or method of manufacture (e.g. different mixing times); 3) different in-process controls, quality tests, or assay methods; 4) production of different batch sizes; 5) employment of different product reprocessing procedures; or 6) employment of a different manufacturing site.

Changes such as these may be proposed or may be implemented during the product development stage, during scale-up of product manufacture before NDA approval, or after NDA approval and product marketing. In all instances, it is critical to assess the impact of the change in meeting the proposed or established standards for product quality (e.g., dissolution rate and bioavailability). It is necessary for a manufacturer to document the change, validate its effect, and provide the necessary information to the FDA. Some changes that are considered minor (as a change in tablet color) and do not affect product quality do not require prior FDA approval for implementation. Other changes that may affect product quality and performance (as use of a substantially different quantity or grade of an excipient, or, use of a piece of manufacturing equipment that changes the basic methodology of manufacture) require prior FDA approval for implementation (29).

Official and Commercially Available Tablets

There are hundreds of tablets recognized by the USP and literally thousands of commercially available tableted products from virtually all pharmaceutical manufacturers, in most therapeutic categories, and in various dosage strengths. Examples of a limited number of these are presented in Table 7.4.

Packaging and Storing Tablets

Tablets are stored in tight containers, in places of low humidity, and protected from extremes in temperature. Products that are prone to decomposition by moisture generally are copackaged with a desiccant packet. Drugs that are adversely affected by light are packaged in light-resistant containers. With a few exceptions, tablets that are properly stored will remain stable for several years or more.

In dispensing tablets, the pharmacist is well advised to use a similar type of container as provided by the manufacturer of the product. The patient is well advised to maintain the drug in the container dispensed. Storage conditions, as recommended for the particular product, should be maintained by the pharmacist and patient alike and expiration dates observed.

The pharmacist should be aware also that the hardness of certain tablets may change upon aging usually resulting in a decrease in the disintegration and dissolution rates of the product. The increase in tablet hardness can frequently be attributed to the increased adhesion of the binding agent and other formulative components within the tablet. Examples of increased tablet hardening with age have been reported for a number of drugs including aluminum hydroxide, sodium salicylate and phenylbutazone (30).

Table 7.4. Examples of Some Official Tablets

Official Tablet	*Some Representative Commercial Products*	*Tablet Strengths*	*Category*
Acetaminophen	Tylenol (McNeil)	325 and 500 mg	Analgesic and antipyretic
Acyclovir	Zovirax (Glaxo Wellcome)	400 and 800 mg	Antiviral
Allopurinol	Zyloprim (Glaxo Wellcome)	100 and 300 mg	Antigout and antiurolithic
Amitriptyline HCl	Elavil HCl (Zeneca)	10, 25, 50, 100, and 150 mg	Antidepressant
Carbamazepine	Tegretol (Novartis)	200 mg	Anticonvulsant
Chlorambucil	Leukeran (Glaxo Wellcome)	2 mg	Antineoplastic
Chlorpropamide	Diabinese (Pfizer)	100 and 250 mg	Antidiabetic
Cimetidine	Tagamet (SmithKline Beecham)	200 and 300 mg	Histamine H_2 receptor antagonist
Ciprofloxacin	Cipro (Bayer)	150, 500 and 750 mg	Antibacterial
Conjugated Estrogens	Premarin (Wyeth-Ayerst)	0.3, 0.625, 0.9, 1.25, and 2.5 mg	Estrogen
Diazepam	Valium (Roche)	2, 5, and 10 mg	Sedative and skeletal muscle relaxant
Digoxin	Lanoxin (Glaxo Wellcome)	0.125, 0.25, and 0.5 mg	Cardiotonic
Enalapril	Vasotec (Merck)	5, 10, and 20 mg	Antihypertensive
Furosemide	Lasix (Hoechst Marion Roussel)	20, 40, and 80 mg	Diuretic and antihypertensive
Griseofulvin	Fulvicin (Schering)	250 and 500 mg	Antifungal
Haloperidol	Haldol (Ortho McNeil)	0.5, 1, 2, 5, 10 and 20 mg	Traquilizer
Ibuprofen	Motrin (McNeil)	100 mg	Analgesic and antipyretic
Levothyroxine Sodium	Synthroid (Knoll)	0.025, 0.05, 0.075, 0.1, 0.125, 0.15, 0.2, and 0.3 mg	Thyroid hormone
Loratadine	Claritin (Schering)	10 mg	Antihistamine
Lovostatin	Mevacor (Merck)	10, 20 and 40 mg	Antihypercholesteremic
Meperidine HCl	Demerol (Sanofi Winthrop)	50 and 100 mg	Narcotic analgesic
Methyldopa	Aldomet (Merck)	125, 250, and 500 mg	Antihypertensive
Nitroglycerin	Nitrostat (Parke-Davis)	0.150, 0.3, 0.4, and 0.6 mg	Antianginal
Penicillin V	Pen Vee K (Wyeth-Ayerst)	250 and 500 mg	Antiinfective
Pergolide Mesylate	Permax (Athena)	0.05, 0.25, and 1 mg	Dopamine receptor agonist
Propanolol	Inderal (Wyeth-Ayerst)	10, 20, 40, 60, and 80 mg	Antianginal, antiarrhythmic, and antihypertensive
Terbutaline Sulfate	Brethine (Novartis)	2.5 and 5 mg	Antiasthmatic
Verapamil HCl	Calan (Searle)	40, 80, and 120 mg	Antihypertensive
Warfarin Sodium	Coumadin (DuPont)	2, 2.5, 7.5, and 10 mg	Anticoagulant

Certain tablets containing volatile drugs, as nitroglycerin, may experience the migration of the drug between tablets in the container resulting in a lack of uniformity among the tablets (31). Further, packing materials, as cotton and rayon, in contact with nitroglycerin tablets may absorb varying amounts of nitroglycerin rendering the tablets subpotent (32). The USP directs that nitrogen tablets be preserved in tight containers, preferably of glass, at controlled room temperature.

The USP further directs that nitroglycerin tablets must be dispensed in the original, unopened container, labeled with the following statement directed to the patient. "Warning: to prevent loss of potency, keep these tablets in the original container or in a supplemental Nitroglycerin container specifically labeled as being suitable for Nitroglycerin Tablets. Close tightly immediately after use" (14).

The pharmacist also should caution patients about the handling of medication when it poses a potential risk. For example and as noted earlier, finasteride tablets are taken by men to treat benign prostatic hyperplasia. Finasteride has the potential to adversely affect a male fetus if absorbed by a pregnant woman through either direct contact with finasteride or possibly through semen. Therefore, a woman who is pregnant or who may become pregnant should not handle finasteride tablets or come into contact with finasteride powder. In addition, when the male patient's sexual partner is pregnant or may become pregnant, the patient should avoid exposure of his partner to semen or he should discontinue use of the drug.

Oral Administration of Solid Dosage Forms

Solid dosage forms for oral administration are best taken by placing the dosage form upon the tongue and swallowing it with a glassful of water or beverage. Taking solid dosage forms with adequate amounts of water is important. Some patients attempt to swallow a tablet or capsule without water, but this can be dangerous because of the possibility that the dry dosage form will lodge in the esophagus. Esophageal ulceration can occur with the dry ingestion of solid dosage forms, particularly when taken just before bedtime. Among the drugs of greatest concern in this regard are: alendronate sodium, aspirin, ferrous sulfate, any nonsteroidal antiinflammatory drug (NSAID), potassium chloride and tetracycline antibiotics.

The proper administration of alendronate sodium tablets (i.e., Fosamax, Merck), for example, calls for the tablets to be taken with a full 6- or 8-ounce glass of plain water upon rising in the morning and at least one-half hour before taking any food, beverage or other medication to prevent local irritation of the esophagus and other upper gastrointestinal mucosa. Further, the patient is instructed to not recline for at least 30 minutes and until after the first food of the day is eaten due to the possibility of refluxing the drug back up into the esophagus.

In general, patients who suffer from gastroesophageal reflux disease must take their medications with adequate amounts of water and avoid reclining for at least an hour to avoid reflux.

The administration of oral medication in relation to meals is very important since the bioavailability and efficacy of certain drugs may be severely affected by food and certain drink. The pharmacist should be knowledgeable of such instances and advise patients accordingly.

As mentioned earlier in this chapter, oral dosage forms that have special coatings (e.g., enteric) or are designed to provide controlled drug release must not be chewed, broken, or crushed to preserve their drug release features.

When an ordinary tablet is crushed or a capsule opened to facilitate ease of administration, any unpleasant drug taste may be partially masked by mixing with custards, yogurt, rice pudding, other soft food, or fruit juice. The patient should be advised to consume the entire drug-food mixture to obtain the full drug dose and the drug should not be pre-mixed and allowed to set, due to stability considerations.

If a patient cannot swallow a solid dosage form, the pharmacist can suggest using an available chewable or liquid form of the drug. If these are not available, an extemporaneously compounded liquid form may be prepared.

Other Solid Dosage Forms for Oral Administration

Lozenges

Lozenges can be made by compression or molding. When compressed, they are made using a tablet machine and large, flat punches. The machine is operated at a high degree of compression to produce lozenges that are harder than ordinary tablets so that they dissolve or disintegrate slowly in the mouth. Medicinal substances that are heat stable may be molded into a hard, sugar candy lozenge by candy-making machines that process a warm, highly concentrated, flavored syrup as the base and form the lozenges by molding and drying.

Lozenges have a special place in the delivery of medication. For example, a lozenge dosage form containing clotrimazole (Mycelex Troche, Bayer), an antifungal agent, is used in the treatment of oropharyngeal candidiasis by the patient allowing the lozenge to slowly dissolve in the mouth, providing salivary levels of the antifungal drug for up to 3 hours. A number of other lozenge dosage forms are available for self-care drugs, e.g., benzocaine, dextromethorphan, phenylpropanolamine, and zinc, to treat self-limiting cough/cold symptoms and minor sore throat.

Pills

By definition, pills are small, round, solid dosage forms containing a medicinal agent and intended to be administered orally. Although the manufacture and administration of pills was at one time quite prevalent, today pills have been replaced by compressed tablets and capsules. A procedure for the extemporaneous preparation of pills on a small-scale may be found in the first edition of this text.

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