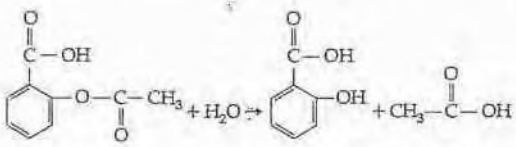
Drug Stability

One of the most important activities of preformulation work is the evaluation of the physical and chemical stability of the pure drug substance. It is essential that these initial studies be conducted using drug samples of known purity. The presence of impurities can lead to erroneous conclusions in such evaluations. Stability studies conducted in the preformulation phase include solid state stability of the drug alone, solution phase stability, and stability in the presence of expected excipients.

Initial investigation begins through knowledge of the drug's chemical structure which allows the preformulation scientist to anticipate the possible degradation reactions.

Chemical instability of medicinal agents may take many forms, because the drugs in use today are of such diverse chemical constitution. Chemically, drug substances are alcohols, phenols, aldehydes, ketones, esters, ethers, acids, salts, alkaloids, glycosides, and others, each with reactive chemical groups having different susceptibilities toward chemical instability. Chemically, the most frequently encountered destructive processes are hydrolysis and oxidation.

Hydrolysis is a solvolysis process in which (drug) molecules interact with water molecules to yield breakdown products of different chemical constitution. For example, aspirin or acetylsalicylic acid combines with a water molecule and hydrolyzes into one molecule of salicylic acid and one molecule of acetic acid:



The process of hydrolysis is probably the most important single cause of drug decomposition mainly because a great number of medicinal agents are esters or contain such other groupings as substituted amides, lactones, and lactams, which are susceptible to the hydrolytic process.

Another destructive process is oxidation. The oxidative process is destructive to many drug types, including aldehydes, alcohols, phenols, sugars, alkaloids, and unsaturated fats and oils.

Chemically, oxidation involves the loss of electrons from an atom or a molecule. Each electron lost is accepted by some other atom or molecule, thereby accomplishing the reduction of the recipient. In inorganic chemistry, oxidation is accompanied by an increase in the positive valence of an element—for example, ferrous (+2) oxidizing to ferric (+3). In organic chemistry, oxidation is frequently considered synonymous with the loss of hydrogen (dehydrogenation) from a molecule. The oxidative process frequently involves free chemical radicals, which are molecules or atoms containing one or more unpaired electrons, as molecular (atmospheric) oxygen (•O—O•) and free hydroxyl (•OH). These radicals tend to take electrons from other chemicals, thereby oxidizing the donor. Many of the oxidative changes in pharmaceutical preparations have the character of autoxidations. Autoxidations occur spontaneously under the initial influence of atmospheric oxygen and proceed slowly at first and then more rapidly as the process continues. The process has been described as a type of chain reaction commencing by the union of oxygen with the drug molecule and continuing with a free radical of this oxidized molecule participating in the destruction of other drug molecules and so forth.

In drug product formulation work, steps are taken to reduce or prevent the occurrence of drug substance deterioration due to hydrolysis, oxidation, and other processes. These techniques are discussed in a later section.

Pharmaceutic Ingredients

In order 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 utilized to dissolve the drug substance, *preservatives* may be added to prevent microbial growth, *stabilizers* may be used to prevent drug decomposition, and *colorants* and *flavorants* added to enhance product appeal. 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 4–2 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 formulation are discussed in Chapter 5, *Peroral Solids, Capsules, Tablets, and Controlled-Release Dosage Forms.*

The reader should also be aware of the *Hand-*

Table 4–2. Examples of Pharmaceutic Ingredients

Ingredient Type	*Definition*	*Examples*
Acidifying Agent	Used in liquid preparations to provide acidic medium for product stability.	acetic acid citric 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
Aerosol Propellant	An agent responsible for developing the pressure within an aerosol container and expelling the product when the valve is opened.	carbon dioxide dichlorodifluoromethane dichlorotetrafluoroethane trichloromonofluoromethane
Air Displacement	An agent which is employed to displace air in a hermetically sealed container to enhance product stability.	nitrogen
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.	benzoic acid butylparaben ethylparaben methylparaben 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

Table 4–2. Continued

Ingredient Type	*Definition*	*Examples*
Antioxidant	An agent which 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
Chelating Agent	A 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.	edetate disodium edetic acid
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

Table 4–2. Continued

Ingredient Type	*Definition*	*Examples*
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	A 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	The 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
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 which 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

Table 4–2. Continued

Ingredient Type	*Definition*	*Examples*
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 which 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

Table 4–2. Continued

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) *enteric coating:* cellulose acetate phthalate shellac (35% in alcohol, "pharmaceutical glaze")
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

Table 4–2. Continued

Ingredient Type	*Definition*	*Examples*
Tonicity Agent	Used to render a solution similar in osmotic characteristics to physiologic fluids. Ophthalmic, parenteral, and irrigation fluids are examples of preparations in which tonicity is a consideration.	dextrose sodium chloride
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

book of Pharmaceutical Excipients,[2] which presents monographs on about 150 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.

There is great interest nowadays 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 generally 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 would facilitate production efficiency, enable the marketing of a single formulation of a product internationally, and enhance regulatory approval of pharmaceutical products worldwide. The goal of harmonization is an ongoing effort undertaken by corporate representatives and international regulatory authorities.

Drug Product Stability

As indicated previously, many pharmaceutic ingredients may be utilized in preparing the desired dosage form of a drug substance. Some of these agents may be used to achieve the desired physical and chemical characteristics of the product or to enhance its appearance, odor, and taste. Other substances may be used to increase the stability of the drug substance, particularly against the hydrolytic and oxidative processes. In each instance, the added pharmaceutic ingredient must be compatible with and must not detract from the stability of the drug substance in the particular dosage form prepared.

There are several approaches to the stabilization of pharmaceutical preparations containing drugs subject to deterioration by hydrolysis. Perhaps the most obvious is the reduction, or better yet, the elimination of water from the pharmaceutical system. Even solid dosage forms containing water-labile drugs must be protected from the humidity of the atmosphere. This may be accomplished by applying a waterproof protective coating over tablets or by enclosing and maintaining the drug in tightly closed containers. It is not unusual to detect hydrolyzed aspirin by noticing an odor of acetic acid upon opening a bottle of aspirin tablets. In liquid preparations, water can frequently be replaced or reduced in the formulation through the use of substitute liquids such as glycerin, propylene glycol, and alcohol. In certain injectable products, anhydrous vegetable oils may be used as the drug's solvent to reduce the chance of hydrolytic decomposition.

Decomposition by hydrolysis may be prevented for other drugs to be administered in liquid form by suspending them in a non-aqueous vehicle rather than by dissolving them in an aqueous solvent. In still other instances, particularly for certain unstable antibiotic drugs, when an aqueous preparation is desired, the drug may be supplied to the pharmacist in a dry form for *reconstitution* by adding a specified volume of purified water just before dispensing. The dry powder supplied commercially is actually a mixture of the antibiotic, suspending agents, flavorants, and colorants, which, when reconstituted by the pharmacist, remains a stable suspension or solution of the drug for the time period in which the preparation is normally consumed. Storage under refrigeration is advisable for most preparations considered unstable due to hydrolytic causes. Together with temperature, pH is a major determinant in the stability of a drug prone to hydrolytic decomposition. The hydrolysis of most drugs is dependent upon the relative concentrations of the hydroxyl and hydronium ions, and a pH at which each drug is optimally stable can be easily determined. For most hydrolyzable drugs the pH of optimum stability is on the acid side, somewhere between pH 5 and 6. Therefore, through judicious use of buffering agents, the stability of otherwise unstable compounds can be increased.

Pharmaceutically, the oxidation of a susceptible drug substance is most likely to occur when it is maintained in other than the dry state in the presence of oxygen, exposed to light, or combined in formulation with other chemical agents without proper regard to their influence on the oxidation process. The oxidation of a chemical in a pharmaceutical preparation is usually attendant with an alteration in the color of that preparation. It may also result in precipitation or a change in the usual odor of a preparation.

The oxidative process is diverted, and the stability of the drug is preserved by agents called *antioxidants,* which react with one or more compounds in the drug to prevent progress of the chain reaction. In general, antioxidants act by providing electrons and easily available hydrogen atoms that are accepted more readily by the free radicals than are those of the drug being protected. Various antioxidants are employed in pharmacy. Among those more frequently used in aqueous preparations are sodium sulfite (Na_2SO_3), sodium bisulfite ($NaHSO_3$), hypophosphorous acid (H_3PO_2), and ascorbic acid. In oleaginous (oily or unctuous) preparations, alphatocopherol, butylhydroxyanisole, and ascorbyl palmitate find application.

In June 1987, FDA labeling regulations went into effect requiring a warning about possible allergic-type reactions, including anaphylaxis in the package insert for prescription drugs to which sulfites have been added to the final dosage form. Sulfites are used as preservatives in many injectable drugs, such as antibiotics and local anesthetics. Some inhalants and ophthalmic preparations also contain sulfites, but relatively few oral drugs contain these chemicals. The purpose of the regulation is to protect the estimated 0.2% of the population who suffer allergic reactions from the chemicals. Many of the sulfite-sensitive persons suffer from asthma or other allergic conditions. Previous to the regulations

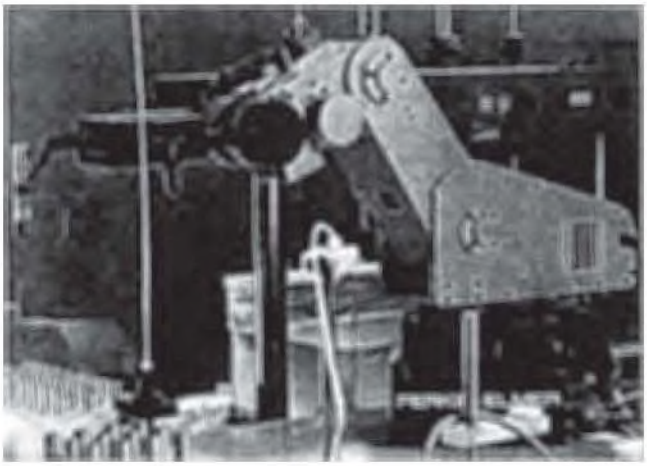


Fig. 4–12. *Robotics in laboratory use. Perkin-Elmer Robotic Arm and Perkin-Elmer Lambda 1a UV/VIS Spectrophotometer. (Courtesy of Elan Corporation, plc.)*

pling, and packaging. Figure 4–12 presents an example of the use of robotics in laboratory use. Laboratory robotics provides automation in such areas as sample preparation and handling, wet chemistry procedures, laboratory process control, and instrumental analysis.[31] Pharmaceutical applications include automated product handling in production lines and in procedures as sampling and analysis, tablet content uniformity, and dissolution testing.

Among the advantages cited for computer use and automation within the pharmaceutical industry are:[32–33]

- increased productivity reducing labor
- improved process and product quality
- reduction in operator error and levels of product rejections
- increased process yields (as from chemical synthesis of drug compounds)
- enhanced repeatability of processes
- improved operator protection due to less "hands on" activity
- automated diagnostic and alarm actions alerting of possible mechanical malfunction, process decontrol or product defect
- assist in process and product validation efforts
- assist in bookkeeping efforts
- assist in scheduling efficacy
- reduced cost per product unit

Movement toward Paperless Electronic Records

There is an effort underway by the FDA and the pharmaceutical industry to replace the traditional use of paper with electronic systems to record, transmit, and maintain needed documentation. This includes records developed by industry to support applications for drug product approvals—e.g., computer assisted new drug applications (CANDAs)—and FDA inspections for CGMP compliance.

Among the regulatory and legal issues involved in the effort toward a paperless system are the authenticity, integrity, and security of electronic records, and the electronic means of replacing conventional handwritten signatures and initials, as required on reports and documents to identify individuals having functional responsibility and operational authority.

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Peroral Solids, Capsules, Tablets, and Controlled-Release Dosage Forms

WHEN MEDICATIONS are to be administered orally in dry form, capsules and tablets are most frequently used. They are effective and provide the patient with convenience of handling, identification, and administration. From a pharmaceutic standpoint, solid dosage forms are generally more stable than are their liquid counterparts and thus are preferred for poorly stable drugs. Dry powders are taken orally (usually after mixing in water) to a much lesser extent than are capsules and tablets, but are preferred by some patients who are unable to swallow the solid dosage forms. However, most medicated powders are utilized as external applications to the skin. While the use of powders *per se* in therapeutics is limited, the use of powders in dosage form preparation is extensive. Most of the medicinal substances in use today occur in crystalline or powdered form and are blended with other powdered materials, as inert fillers and disintegrants, prior to fabrication into solid dosage forms. Powdered drugs are also frequently added to ointments, pastes, suppositories, and other dosage forms during their preparation. Similarly, granules, which are agglomerates of powdered materials prepared into larger free flowing particles, are utilized chiefly in the preparation of tablets and in dry preparations intended to be reconstituted to liquid forms prior to use by the addition of the appropriate vehicle.

Powders

As a pharmaceutical preparation, a *powder* (Latin, *pulvis*) is a mixture of finely divided drugs and/or chemicals in dry form. This should be differentiated from the general use of the term "powder" or "powdered" which is commonly used to describe the physical state of a single chemical substance or a single drug.

A powder may be a finely subdivided preparation, a coarsely comminuted product, or a product of intermediate particle size. It may be prepared from a naturally occurring dried vegetable drug, or it may be a physical admixture of two or more powdered pure chemical agents present in definite proportions. Powders may contain small proportions of liquids dispersed thoroughly and uniformly over the solid components of the mixture, or the powder may be composed entirely of solid materials.

Some powders are intended to be used internally; others, externally. Certain powders are dispensed by the pharmacist to the patient in bulk quantities; others, in divided, individually packaged portions, depending primarily on the use, dose, or potency of the powder.

The disadvantages of powders as a dosage form include the potential for patient misunderstanding of the correct method of use, the undesirability of taking bitter or unpleasant tasting drugs in this manner, the difficulty of protecting from decomposition powders containing hygroscopic, deliquescent, or aromatic materials, and the manufacturing expense required in the preparation of uniform individually wrapped doses of powders. To be of high efficacy, the powder must be a homogeneous blend of all of the components and must be of the most advantageous particle size. As noted earlier (Chapter 3), the particle size of a drug not only contributes to its rate of solubility in a glass of water or within the stomach or intestine, but also may influence its biologic availability.

Particle Size and Analysis

The particles of pharmaceutical powders may be very coarse, of the dimensions of about 10,000 microns or 10 mm, or they may be extremely fine, approaching colloidal dimensions of 1 micron or less. In order to standardize the particle size of a given powder, the USP employs descriptive terms such as "Very Coarse, Coarse, Moderately Coarse, Fine, and Very Fine," which are related to the proportion of powder that is capable of passing through the openings of standardized sieves of varying dimensions in a specified time

Table 5–1. Opening of Standard Sieves*

Sieve Number	*Sieve Opening*
2	9.5 mm
3.5	5.6 mm
4	4.75 mm
8	2.36 mm
10	2.00 mm
20	850 μm
30	600 μm
40	425 μm
50	300 μm
60	250 μm
70	212 μm
80	180 μm
100	150 μm
120	125 μm
200	75 μm
230	63 μm
270	53 μm
325	45 μm
400	38 μm

* Adapted from USP23-NF18.

period under shaking, generally in a *mechanical sieve shaker*. Table 5–1 presents the Standard Sieve Numbers and the sieve openings in each, expressed in millimeters and in micrometers. Sieves for such pharmaceutical testing and measurement are generally made of wire cloth woven from brass, bronze, or other suitable wire. They are not coated or plated.

Powders of vegetable and animal drugs are officially defined as follows:[1]

Very Coarse (or a No. 8) powder—All particles pass through a No. 8 sieve and not more than 20% through a No. 60 sieve.

Coarse (or a No. 20) powder—All particles pass through a No. 20 sieve and not more than 40% through a No. 60 sieve.

Moderately Coarse (or a No. 40) powder—All particles pass through a No. 40 sieve and not more than 40% through a No. 80 sieve.

Fine (or a No. 60) powder—All particles pass through a No. 60 sieve and not more than 40% through a No. 100 sieve.

Very Fine (or a No. 80) powder—All particles pass through a No. 80 sieve. There is no limit as to greater fineness.

The powder fineness for chemicals is defined as follows. It should be noted that there is no "Very Coarse" category.

Coarse (or a No. 20) powder—All particles pass through a No. 20 sieve and not more than 60% through a No. 40 sieve.

Moderately Coarse (or a No. 40) powder—All particles pass through a No. 40 sieve and not more than 60% through a No. 60 sieve.

Fine (or a No. 80) powder—All particles pass through a No. 80 sieve. There is no limit as to greater fineness.

Very Fine (or a No. 120) powder—All particles pass through a No. 120 sieve. There is no limit as to greater fineness.

Granules typically fall within the range of 4- to 12-sieve size, although granulations of powders prepared in the 12- to 20-sieve range are not uncommon when used in tablet making.

The purpose of particle size analysis in pharmacy is to obtain quantitative data on the size, distribution, and shapes of drug and nondrug components to be used in pharmaceutical formulations. There may be substantial differences in particle size, crystalline type, and amorphous shape within and between substances. Particle size can influence a variety of important factors:

- *Dissolution rate* of particles intended to dissolve;
- *Suspendability* of particles intended to remain undissolved but uniformly dispersed in a liquid vehicle (e.g., fine dispersions have particles of from approximately 0.5 to 10 micrometers or μm);
- *Uniform distribution* of a drug substance in a powder mixture or solid dosage form;[2]
- *Penetrability* of particles intended to be inhaled to reach a desired location within the respiratory tract (e.g., 1–5 micrometers) for deposition deep in the respiratory tract);[3] and the
- *Nongrittiness* of solid particles in dermal ointments, creams, and ophthalmic preparations (e.g., fine powders may be 50–100 micrometers in size).

A number of methods exist for the determination of particle size, including the following:

- *Sieving*, in which particles are passed by mechanical shaking through a series of sieves of known and successively smaller size and the determination of the proportion of powder passing through or being withheld on each sieve (range: from about 50 to 3360 micrometers, depending upon sieve sizes).[4]
- *Microscopy*, in which the particles are sized through the use of a calibrated grid background or other measuring device (range: 0.2 to 100 micrometers).[5,6]

Micromeritics

Micromeritics is the science of small particles; a *particle* is any unit of matter having defined physical dimensions. It is important to study particles because the majority of drug dosage forms are solids; solids are not "static" systems—the physical state of particles can be altered by physical manipulation and particle characteristics can alter therapeutic effectiveness.

Micromeritics includes a number of characteristics including particle size, particle size distribution, particle shape, angle of repose, porosity, true volume, bulk volume, apparent density and bulkiness.

PARTICLE SIZE

A number of techniques can be used for determining particle size and particle size distributions. Particle size determinations are complicated by the fact that particles are nonuniform in shape. Only two relatively simple examples will be provided for a detailed calculation of the average particle size of a powder mixture. Other methods will be generally discussed. The techniques utilized will include the microscopic method and the sieving method.

The *microscopic method* can include counting not less than 200 particles in a single plane using a calibrated ocular on a microscope. Given the following data, what is the average diameter of the particles?

Size Group of Counted Particles (μ)	Middle Value μ "d"	No. Particles Per Group "n"	*"nd"*
40–60	50	15	750
60–80	70	25	1750
80–100	90	95	8550
100–120	110	140	15400
120–140	130	80	10400
		$\Sigma n = 355$	$\Sigma nd = 36850$

$$d_{av} = \frac{\Sigma nd}{\Sigma n} = \frac{36{,}850}{355} = 103.8\ \mu$$

The *sieving method* involves using a set of U.S. Standard sieves in the size range desired. A stack of sieves is arranged in order, the powder placed in the top sieve, the stack shaken, the quantity of powder resting on each sieve weighed, and the following calculation performed.

Sieve No.	*Arithmetic Mean Opening (mm)*	*Weight Retained (G)*	*% Retained*	*% Retained × Mean Opening*
20/40	0.630	15.5	14.3	9.009
40/60	0.335	25.8	23.7	7.939
60/80	0.214	48.3	44.4	9.502
80/100	0.163	15.6	14.3	2.330
100/120	0.137	3.5	3.3	0.452
		108.7	100.0	29.232

$$d_{av} = \frac{\Sigma\ (\%\ \text{retained}) \times (\text{ave size})}{100} = \frac{29.232}{100} = 0.2923\ \text{mm}$$

Another method of particle size determination involves *sedimentation* using the "Andreasen Pipet." The Andreasen pipet is a special cylindrical container designed such that a sample can be removed from the lower portion at selected time intervals. The powder is dispersed in a nonsolvent in the Andreasen Pipet, agitated, and 20 mL samples removed over a period of time. Each 20 mL sample is dried and weighed. Using the following equation, the particle diameters can be calculated.

$$d = \frac{18\ h\eta}{(\rho_i - \rho_e)\ gt}$$

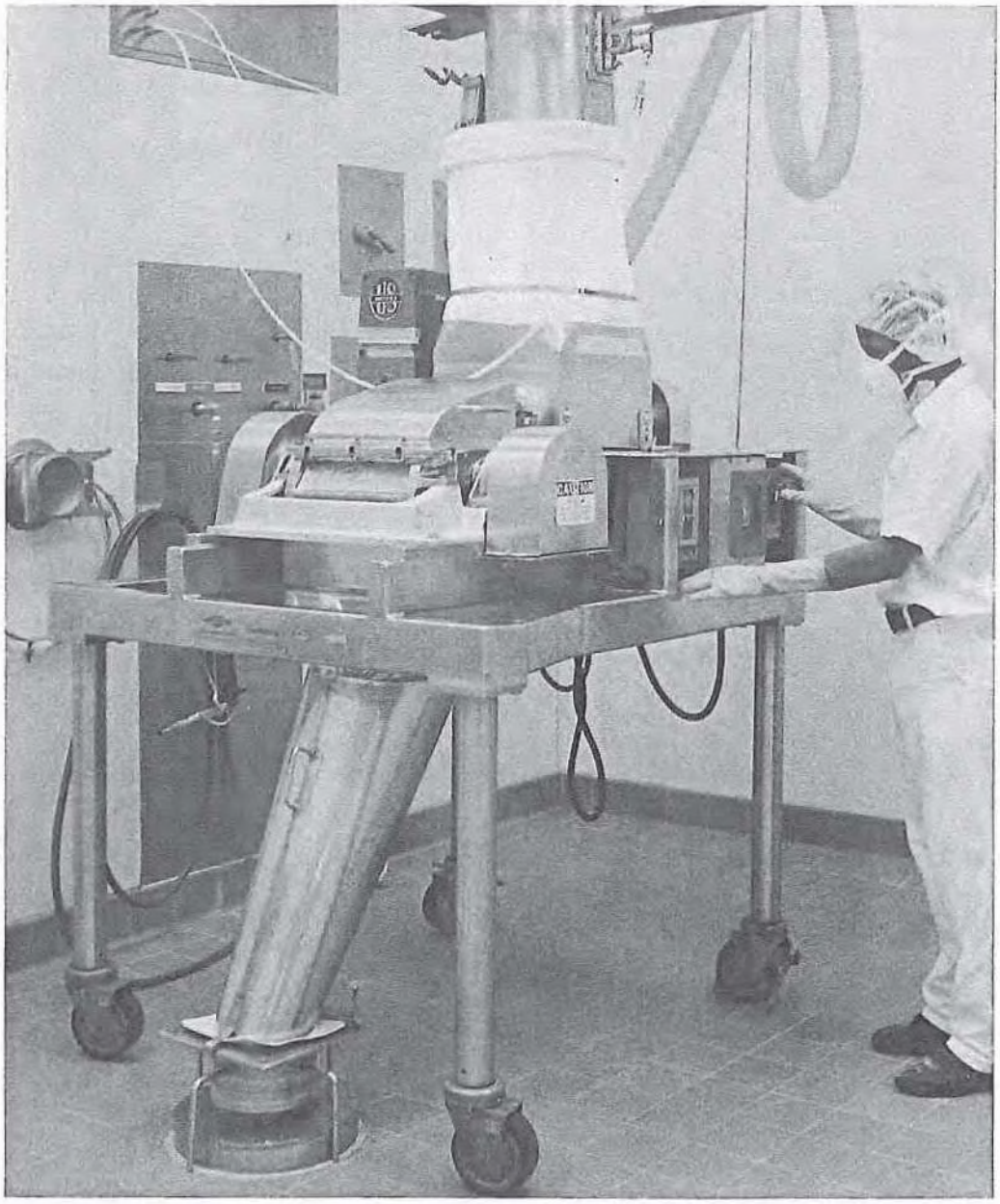

Fig. 5–47. *Frewitt Oscillator or Fitz Mill utilized in the pulverization or granulation process. (Courtesy of Eli Lilly and Company.)*

a tablet deduster. An example of this type of apparatus are shown in Figure 5–49.

Tablet Coating

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

Some tablets are coated to prevent inadvertent contact with the drug substance and the conse-

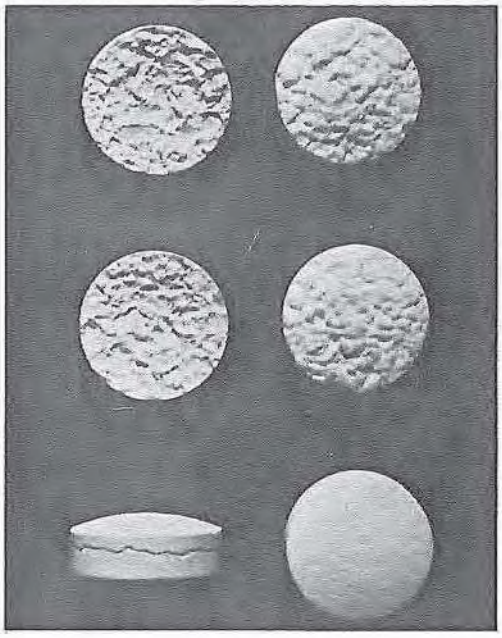

Fig. 5–48. *Tablets which have split on aging, due to conditions of manufacture or storage.*

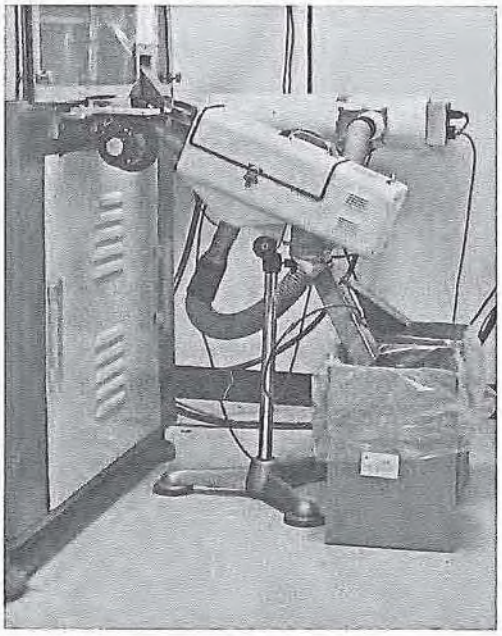

Fig. 5–49. *Model 25 Manesty Tablet Deduster. Tablets leaving tableting machine are dedusted and passed into collection containers. (Courtesy of Eli Lilly and Company.)*

quent effects of drug absorption. Proscar (finasteride, Merck) tablets, for example, 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 or through sexual contact, by virtue of traces of drug in semen. If finasteride is absorbed by a woman who is pregnant with a male baby, the drug has the capacity to cause abnormalities in the child's sex organs.

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. Generally the entire coating process is conducted in a series of mechanically operated coating pans, which are acorn-shaped vessels of galvanized iron, stainless steel, or copper partially open in the front and with diameters ranging from about 1 to 4 feet and therefore of various capacities (Figs. 5–50 and 5–51). The smaller pans are used for experimental, developmental, and pilot plant operations; the larger pans, for industrial production. The pans are fixed and operate at about a 40° angle, which permits the tablets to remain inside the pan during its revolutions yet also permits the operator to observe and handle the tablets from the open end of the pan. During each of the operations involved in the coating of tablets, the pan is rotated by a motor at moderate speeds, allowing the tablets to tumble and roll about in the pan and make contact with each other and with the coating solutions. As they rotate, the coating solution is gently poured or sprayed onto the tablets in portions, with warm air introduced to hasten the drying of the coat. Tablets may require a number of coats of material, with each coat applied only after the previous coat has dried. Tablets intended to be coated are generally compressed tablets that have been prepared to be highly convex and have as thin an edge as possible to permit the coatings to form rounded rather than angular edges.

WATERPROOFING AND SEALING COATS. For tablets containing components that may absorb moisture or be adversely affected on contact with

Fig. 5–50. *Tablet coating, an older style coating pan, showing the warm air supply and the exhaust. (Courtesy of Wyeth Laboratories.)*

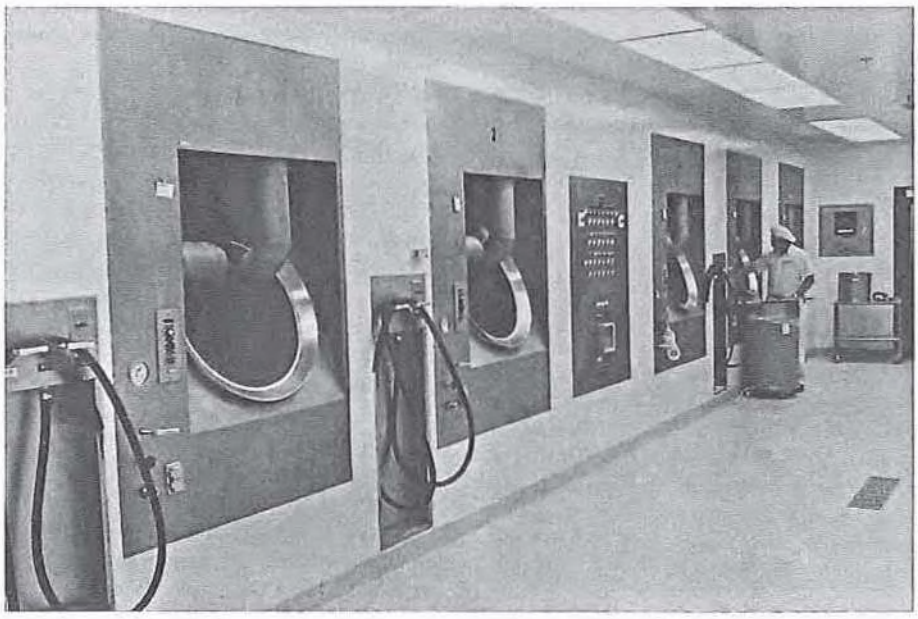

Fig. 5–51. *Modern tablet coating facility. Air and exhaust ducts to assist drying are automatically operated from central board. (Courtesy of Eli Lilly and Company.)*

moisture, a waterproofing layer or coating of a material such as shellac is placed on the compressed tablets before the subcoating application. The shellac or other waterproofing agent is applied in solution (usually alcoholic) form and is gently poured on the compressed tablets rotating in the coating pans or is sprayed on as a fine spray. Warm air is blown into the pan during the coating to hasten the drying and to prevent tablets from sticking together. A second coat of the waterproofing substance may be added to the tablets after the first coat has dried to ensure against moisture penetration into the compressed tablets.

SUBCOATING. After the waterproofing or sealing coats (if they are necessary) have been applied, the tablets are given about 3 to 5 subcoats of a sugar-based syrup for the purpose of rounding the tablets and bonding the sugar coating to the compressed tablet. In applying the subcoating, a heavy syrup generally containing gelatin or polyvinylpyrollidone (PVP), or sometimes acacia is added to the tablets as they roll in the coating pan. When the tablets are partially dry they are sprinkled with a dusting powder, which is usually a mixture of powdered sugar and starch but may also contain talc, acacia, or precipitated chalk. Warm air is applied to the rolling tablets, and when they are dry, the subcoating process is repeated and repeated again until the tablets are of the desired shape and size (Fig. 5–52). At this point, the tablets are usually removed from the coating pan, the excess powder is shaken off the tablets by gently jostling them on a cloth screen, and the coating pan is then washed to remove extraneous coating material.

Fig. 5–52. *Tablet gauge used to measure the size of coated tablets. (Courtesy of Eli Lilly and Company.)*

SMOOTHING AND FINAL ROUNDING. After the tablets have been subcoated to the desired shape (roundness), 5 to 10 additional coatings of a very thick syrup are applied to the rolling tablets for the purpose of completing the rounding of the tablets and smoothing the coatings. This syrup may be composed of a sucrose-based simple syrup, or it may have additional components like 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 sticking of the tablets to one another. A dusting powder may or may not be used between syrup applications, but warm air is generally applied to hasten the drying time of each coat. If the coating is to be colored, the suitable dye may be added to the syrup during this step of the coating process as well as during the next step.

FINISHING AND COLORING. To attain final smoothness and the appropriate color to the tablets, several coats of a thin syrup containing the desired colorant (if any) are applied. This step is usually performed in a clean pan, free from previous coating materials.

IMPRINTING. Solid dosage forms may be passed through special imprinting machines (Fig. 5–53) 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 most clinical investigations; drugs 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 infeasible.

Code imprints, in conjunction with a product's size, shape, and color, permit the unique identification of a drug product and its manufacturer or distributor. Code imprints may contain any combination of letters and numbers, or the product's National Drug Code number, and any marks, symbols, logos, or monograms assigned by the drug company to the product. Each product's imprint must be registered with the FDA.

Technically, the imprint may be *debossed, em-*

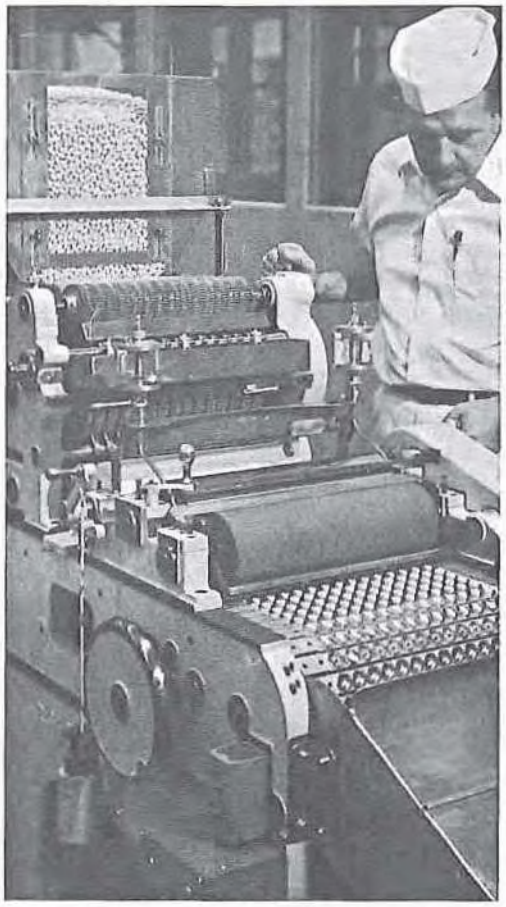

Fig. 5–53. *Branding of coated compression tablets on a Hartnett branding machine. (Courtesy of The Upjohn Company.)*

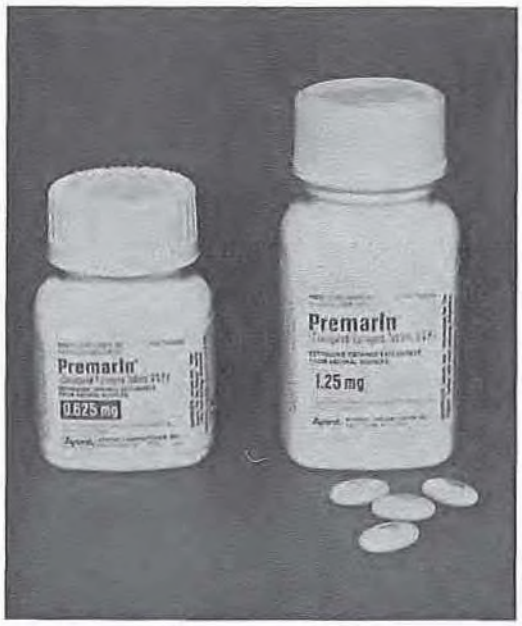

Fig. 5–54. *Example of coated, polished, and monogrammed tablets. (Courtesy of Wyeth-Ayerst Laboratories.)*

bossed, 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 after it has been fabricated.

POLISHING. Coated tablets may be polished in special drum-shaped pans made by stretching a cloth fabric over a metal frame or in ordinary coating pans lined with canvas. The fabric or the canvas may be impregnated with a wax such as carnauba wax with or without the addition of beeswax and the tablets polished as they roll about in the pan. Or, the wax may be dissolved in a nonaqueous solvent such as acetone or petroleum benzin and sprayed on the rolling tablets in small amounts. After each coat has dried, the addition of a small amount of talc to the tumbling tablets contributes to their high luster (Fig. 5–54). Two or three coats of wax may be applied depending upon the desired gloss. Another method of polishing tablets simply involves placing pieces of wax in the polishing pan along with the tablets and permitting the tablets to tumble over the wax until the desired sheen is attained.

Film-Coating Tablets

As one can ascertain from the previous discussion of sugarcoating, the process is not only tedious and time-consuming, requiring the expertise of a highly skilled technician, but it also results in the preparation of coated tablets that may be twice the size and weight of the original uncoated compressed tablets. These factors are important to a manufacturer in his consideration of the expense of both packaging materials and shipping. From a patient's point of view, large tablets are not as convenient to swallow as are small tablets. Also, the coating of tablets by the application of the sugarcoating may vary slightly from batch to batch and within the batch. 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. The coating is thin enough to reveal any depressed or raised monograms punched into the tablet by the tablet punches. In addition, film-coated tablets are far more resistant to destruction by abrasion than are sugar-coated tablets, and 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 generally 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, F.D.&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 upon 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 problem of the release of these potentially toxic agents into the atmosphere, the high cost of solvent recovery systems, and their explosiveness, pharmaceutical manufacturers are favoring 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 film-coating solutions. One commercially available (to the pharmaceutical industry) water-based, colloidal coating dispersion, is called AQUACOAT® (FMC Corporation) and contains a 30% ethyl cellulose pseudolatex. Pseudolatex dispersions have the advantage of high solids content (for greater coating ability) and 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. In using the pseudolatex coating dispersion, a plasticizer is incorporated to assist in the production of a denser, less-permeable film, with higher gloss and greater mechanical strength. Other aqueous systems utilized to film-coat tablets include the use of cellulosic materials as methylcellulose, hydroxypropyl cellulose, and hydroxypropyl methylcellulose.

A typical aqueous film-coating formulation contains the following:[21]

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, 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.[21]

Enteric Coating

The purpose of enteric coating for solid dosage forms has already been discussed. The design of an enteric coating may be based upon the transit time required for the passage of the dosage form from the stomach into the intestines. This may be accomplished through coatings of sufficient thickness to resist dissolution in the stomach. More usually, an enteric coating is based upon the pH of the environment, being designed to resist 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 so long as the coating material resists breakdown in the gastric fluid.

Among the materials used in enteric coatings are shellac, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, and cellulose acetate phthalate.

Fluid-Bed or Air Suspension Coating

This process, utilizing equipment of the type shown in Figure 5–55, involves the spray coating of pellets, beads, granules, powders, or tablets held in suspension by a column of air. The fluid bed processing equipment used is multifunctional and may be used in preparing tablet granulations as well, as noted earlier in this chapter.

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.

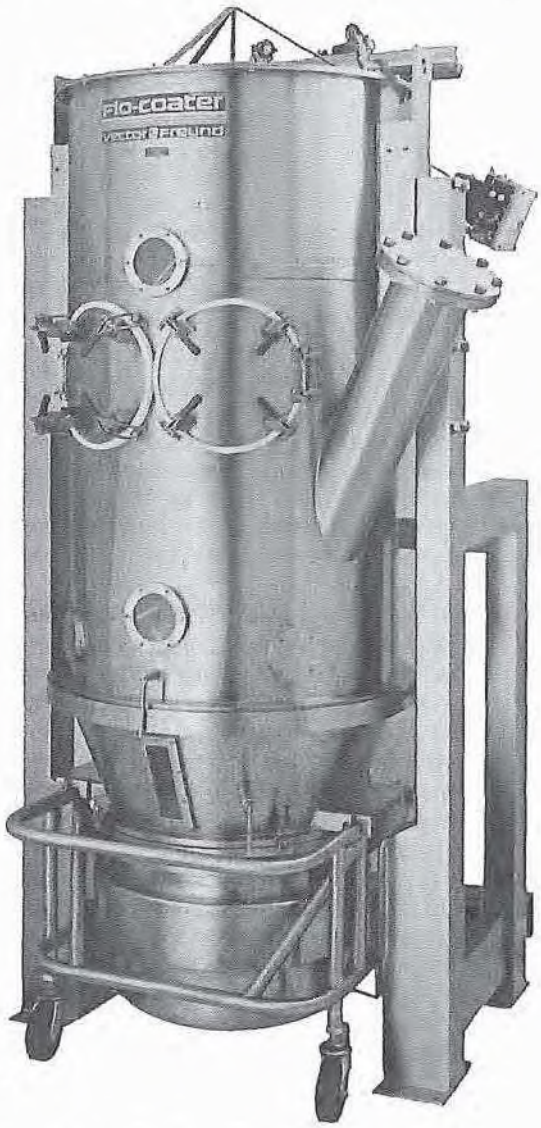

Fig. 5–55. *Vector/Freund Flo-Coater production system. A fluid bed system used in the application of coatings to beads, granules, powders, and tablets. Capacity of models ranges from 5 kg to 700 kg. (Courtesy of Vector Corporation.)*

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.[22] Both the top-spray and bottom-spray methods

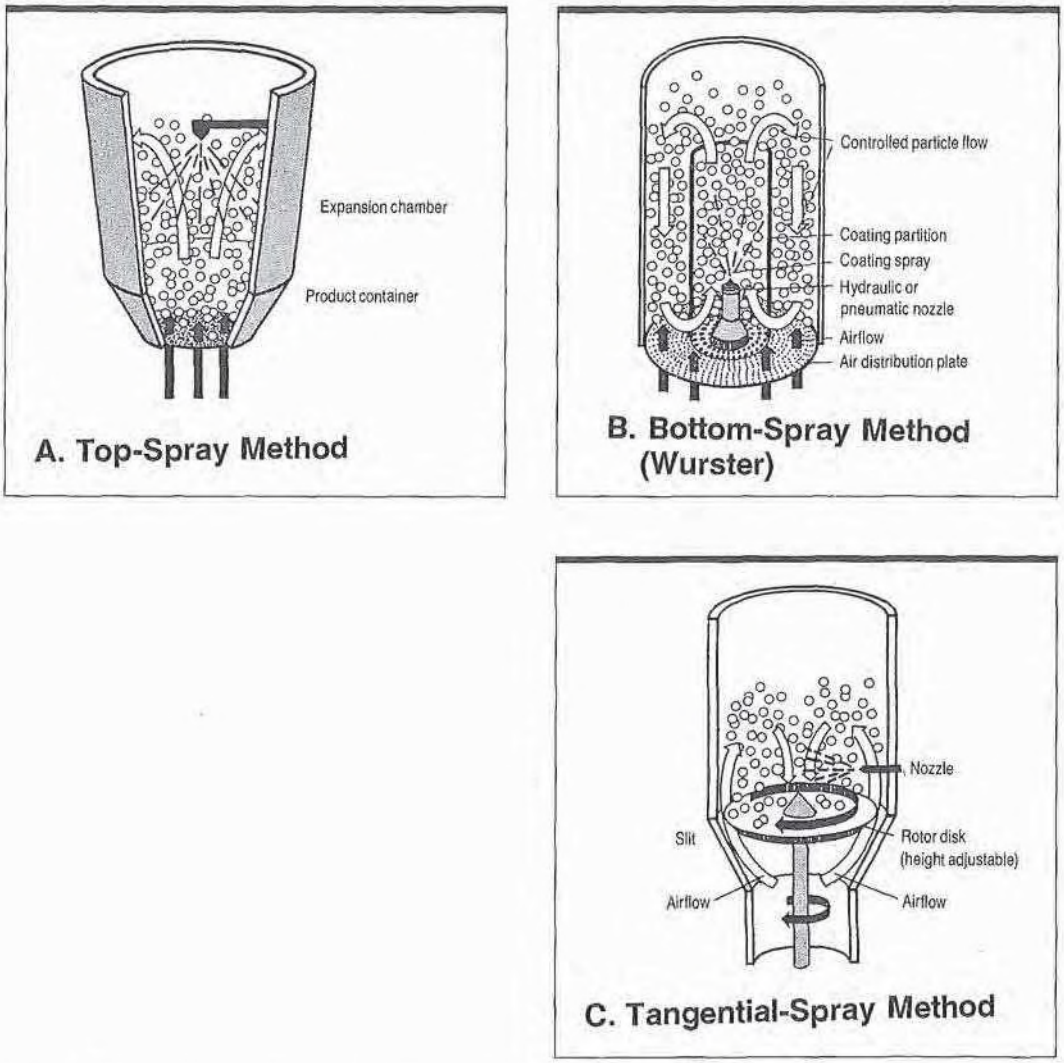

Fig. 5–56. *(A) Top-spray, (B) bottom-spray (Wurster), and (C) tangential-spray methods in the fluid-bed coating of solid particles. (Courtesy of Glatt Air Techniques, Inc.)*

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 5–56.

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.[22,23] 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.[23]

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.[23]

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 a powder is compressed onto a tablet core of drug with a special tablet press. This method eliminates the time-consuming and tedious operation previously described in this section. Compression coating is an anhydrous operation and thus may be safely employed in the coating of tablets having a drug that is sensitive to moisture. The resulting coat is more uniform than the usual sugarcoating applied using pans, and less of a coating is required. Resulting tablets are lighter and smaller and are therefore 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. 5–57).

Fig. 5–57. *Checking for physical imperfections in coated tablets. (Courtesy of Smith, Kline & French.)*

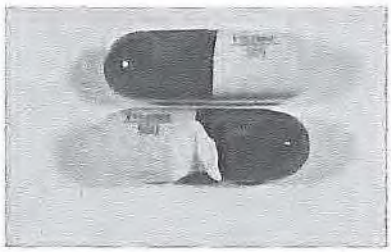

Fig. 5–58. *Cut-away view of "Gelcaps" dosage form. A gelatin-coated capsule-shaped tablet. Dosage form is more easily swallowed than a comparable tablet, smaller than an equivalent capsule, and tamper-evident. (Courtesy of McNeil Consumer Products Co.)*

Gelatin Coated Tablets

A recent innovation in tablet coating is the gelatin-coated tablet. Termed GELCAPS®, the innovator product is a gelatin-coated capsule-shaped tablet (Fig. 5–58). The use of a tablet makes the size of the product about one-third smaller than a capsule filled with an equivalent amount of powder. The gelatin coating facilitates ease of swallowing. Compared to dry-filled, unsealed capsules, GELCAPS are more tamper-resistant and tamper-evident.

Chewable Tablets

Chewable tablets are tablets which are intended to disintegrate smoothly in the mouth at a moderate rate, either with or without actual chewing. Characteristically, chewable tablets have a smooth texture upon disintegration, are pleasant tasting, and leave no bitter or unpleasant aftertaste. Mannitol, a white crystalline hexahydric alcohol, which possesses many of the characteristics desired for the excipient in chewable tablets, is widely employed for this purpose. Mannitol is about 70% as sweet as sucrose with a cool taste and mouth-feel, the latter resulting from its negative heat of solution and a moderate solubility in water. Mannitol's nonhygroscopicity also makes it an ideal excipient for the preparation of chewable tablets containing moisture-sensitive drugs. Chewable tablets are prepared by wet granulation and compression, using minimum degrees of tablet hardness. 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 and glucose, may be substituted f[illegible] lubricants and

binders which do not detract from the texture or desired hardness of the tablet are used in formulating chewable tablets. To enhance the appeal of the tablets, colorants and tart or fruity flavorants are commonly employed. Among the types of products prepared into chewable tablets are antacids and vitamins, analgesic and cold tablets intended for children.

The following is a formula for a typical chewable antacid tablet:[24]

	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.

Official Tablets

Examples of official tablets are presented in Table 5–4.

Rate-Controlled Dosage Forms and Drug Delivery Systems

Some solid dosage forms are designed to release their medication to the body for absorption rapidly and completely, whereas other products are designed to release the drug slowly for more prolonged drug release and sustained drug action. The latter types of dosage forms are commonly referred to as *controlled-release, sustained-release, prolonged-release, timed-release, slow-release, sustained-action, prolonged-action, extended-action,* or *rate-controlled* tablets or capsules.

Although these terms have been frequently used interchangeably, the meaning of "sustained-release" and "controlled-release" are different. Sustained release describes the release of a drug substance from a dosage form or delivery system over an extended period of time. Controlled-release describes a system in which the *rate* of the drug's release is more precisely controlled compared to the sustained release product.

The term "drug delivery systems" refers to the technology utilized to present the drug to the desired body site for drug release and absorption. The modern transdermal patch, discussed in Chapter 10 is an example of a drug delivery system. The first drug delivery system developed was the *syringe,* invented in 1855, used to deliver medication by injection.

The goal of rate-controlled technology is to produce a convenient, generally self-administered dosage form that yields a constant infusion of the drug. The advantages of rate-controlled drug delivery are presented in Table 5–5.

Controlled-release dosage forms that provide sustained drug release require less frequent drug administration than ordinary dosage forms (Fig. 5–59A). This is considered an advantage in assuring patient compliance in the taking of medication. Patients required to take 1 or 2 dosage units a day are less likely to forget a dose than if they were required to take their medication 3 or 4 times a day.[25] Further, controlled-release dosage forms allow whole day coverage and help to reduce the need for the patient to be awakened for a night-time dose. Also, depending upon the medication and the dosage form, the daily cost to the patient may be less with less frequent dosage administration.

Rather than providing *sustained-release,* some solid dosage forms are designed to sequentially release two full doses of a drug. Such dosage forms also enable the patient to be maintained on the drug for longer than usual periods following the administration of a single dosage unit. These types of products are usually termed *repeat-action* tablets or capsules (Fig. 5–59B).

Many of these specialized types of dosage forms are protected by patents and have been given trademark names that help to identify both the manufacturer and the type of pharmaceutical product.

Sustained-Release Forms

Most sustained-release forms are designed so that the administration of a single dosage unit provides the immediate release of an amount of drug that promptly produces the desired therapeutic effect and gradual and continual release of additional amounts of drug to maintain this

Table 5–4. Examples of Some Official Tablets

Official Tablet	*Some Representative Commercial Products*	*Tablet Strengths Usually Available*	*Category and Comments*
Acetaminophen	Tylenol (McNeil)	325 mg	Analgesic and antipyretic
Allopurinol	Zyloprim (Burroughs Wellcome)	100 and 300 mg	Antigout; antiurolithic
Amitriptyline HCl	Elavil HCl (Stuart)	10, 25, 50, 100, and 150 mg	Antidepressant
Bisacodyl	Dulcolax (Ciba)	5 mg	Cathartic; enteric coated tablets
Carbamazepine	Tegretol (Basel)	200 mg	Anticonvulsant
Chlorambucil	Leukeran (Burroughs Wellcome)	2 mg	Antineoplastic
Chlorpheniramine Maleate	Chlor-Trimeton Maleate (Schering-Plough)	4, 8, and 12 mg	Antihistaminic; some tablets (8 and 12 mg) controlled-release
Chlorpropamide	Diabinese (Pfizer)	100 and 250 mg	Antidiabetic
Cimetidine	Tagament (SmithKline Beecham)	200 and 300 mg	Histamine H_2 receptor antagonist
Diazepam	Valium (Roche)	2, 5, and 10 mg	Sedative; skeletal muscle relaxant
Digoxin	Lanoxin (Burroughs Wellcome)	0.125, 0.25, and 0.5 mg	Cardiotonic
Dimenhydrinate	Dramamine (Upjohn)	50 mg 25 and 30 mg	Antinauseant Bronchodilator; vasoconstrictor
Furosemide	Lasix (Hoechst-Roussel)	20, 40, and 80 mg	Diuretic; antihypercalemic; antihypertensive
Griseofulvin	Fulvicin U/F (Schering)	250 and 500 mg	Antifungal
Haloperidol	Haldol (McNeil)	0.5, 1, 2, 5, 10 and 20 mg	Tranquilizer
Hydrochlorothiazide	Hydro-Diuril (Merck & Co.)	25, 50, and 100 mg	Diuretic; antihypertensive
Ibuprofen	Motrin (Upjohn)	300, 400, 600, and 800 mg	Analgesic; antipyretic
Levodopa	Larodopa (Roche)	100, 250, and 500 mg	Antidyskinetic
Levothyroxine sodium	Synthroid (Boots)	0.025, 0.05, 0.075, 0.1, 0.125, 0.15, 0.2, and 0.3 mg	Thyroid hormone
Meclizine HCl	Antivert (Roerig)	12.5, 25, and 50 mg	Antivertigo
Meperidine Hydrochloride	Demerol (Sanofi Winthrop)	50 and 100 mg	Narcotic analgesic
Meprobamate	Equanil (Wyeth-Ayerst)	200 and 400 mg	Sedative; hypnotic
Methyldopa	Aldomet (Merck & Co.)	125, 250, and 500 mg	Antihypertensive
Metronidazole	Flagyl (Searle)	250 and 500 mg	Antiamebic; antitrichomonal
Nitroglycerin	Nitrostat (Parke-Davis)	0.150, 0.3, 0.4, and 0.6 mg	Anti-anginal sublingual tablets
Penicillin V Potassium	Pen Vee (Wyeth-Ayerst)	250 and 500 mg	Antibacterial
Prednisone	Deltasone (Upjohn)	1 mg	Adrenocorticoid
Prochlorperazine Maleate	Compazine (SmithKline Beecham)	5, 10, and 25 mg	Antiemetic
Propanolol HCl	Inderal (Wyeth-Ayerst)	10, 20, 40, 60, 80, and 90 mg	Antianginal; antiarrhythmic; antihypertensive
Sulindac	Clinoril (Merck & Co.)	150 and 200 mg	Antirheumatic, antiinflammatory
Terbutaline sulfate	Brethine (Geigy)	2.5 and 5 mg	Antiasthmatic
Tolbutamide	Orinase (Upjohn)	250 and 500 mg	Antidiabetic
Warfarin Sodium	Coumadin (DuPont)	2, 2	

Table 5–5. Advantages of Rate-Controlled Drug-Delivery Systems Over Conventional Dosage Forms

Advantage	*Explanation*
Reduction in drug blood level fluctuations	By controlling the rate of drug release, "peaks and valleys" of drug-blood or -serum levels are eliminated.
Reduction in dosing frequency	Rate-controlled products deliver more than a single dose of medication and thus are taken less often than conventional forms.
Enhanced patient convenience and compliance	With less frequency of dose administration, the patient is less apt to neglect taking a dose. There is also greater patient convenience with daytime and nighttime medication, and control of chronic illness.
Reduction in adverse side effects	Because there are seldom drug blood level peaks above the drug's therapeutic range, and into the toxic range, adverse side effects are less frequently encountered.
Reduction in health care costs i.e., economy	Although the initial cost of rate-controlled drug delivery systems is usually greater than conventional dosage forms, the average cost of treatment over an extended time period may be less. With less frequency of dosing, enhanced therapeutic benefit, and reduced side-effects, the time required of health care personnel to dispense, administer and monitor patients is reduced.

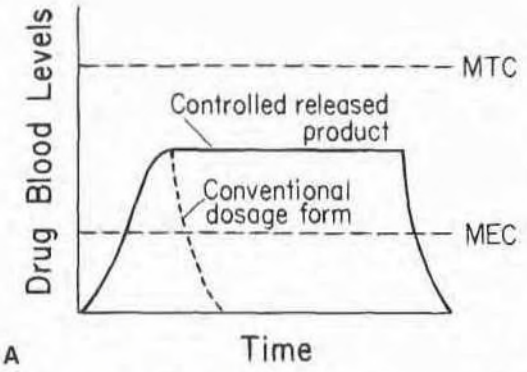

Fig. 5–59A. *Hypothetical drug blood level-time curves for a conventional solid dosage form and a controlled release product.*

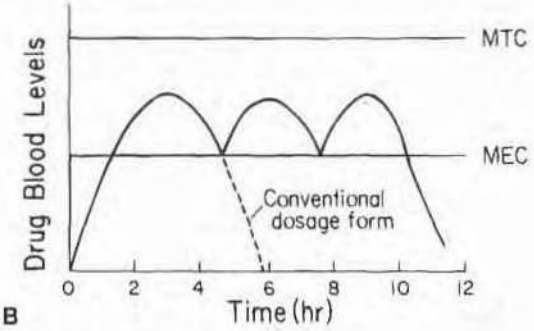

Fig. 5–59B. *Hypothetical drug blood level-time curves for a conventional solid dosage form and a multiple-action product.*

level of effect over an extended period, usually 8 to 12 hours.

In this type of dosage form, the design is based on the particular qualities of each individual drug. What may be an effective type of dosage form design for one drug may be ineffective in promoting the sustained release of another drug because of peculiar physical, chemical, and biological qualities. To maintain the constant level of drug in the system, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. For each drug, this is a highly individualized quality. In general, the drugs best suited for incorporation into a sustained release product have the following characteristics.

1. *They exhibit neither very slow nor very fast rates of absorption and excretion.* Drugs with slow rates of absorption and excretion are usually inherently long-acting and their preparation into sustained-action type dosage forms is not necessary. Similarly, a drug with a short half life, i.e., <2 hours, should not be formulated into a sustained release product because such a delivery system would require unacceptably large release rates and doses.
2. *They are uniformly absorbed from the gastrointestinal tract.* Drugs absorbed poorly or at varying and unpredictable rates are not good candidates for sustained-release products, because their drug release and therefore drug absorption will fluctuate, depending upon the position of the d

testinal tract and the dosage form's rate of movement within the tract.

3. *They are administered in relatively small doses.* Drugs with large single doses frequently are not suitable for the preparation of the sustained-action product because the individual dosage unit needed to maintain the extended therapeutic blood level of the drug would have to be too large for the patient to easily swallow.
4. *They possess a good margin of safety.* The most widely used measure of the margin of safety is its therapeutic index, i.e., median toxic dose, TD50/median effective dose, ED50. This index can range from one (where the effective dose produces toxic effects) to several thousand. For very "potent" drugs when therapeutic concentration is narrow, the value of the therapeutic index is very small. The larger the therapeutic index the safer the drug. Thus, those drugs which are potent in very small doses or possess very narrow or small therapeutic indices are poor candidates for formulation into controlled-release formulations because of technologic limitations of precise control over release rates.
5. *They are used in the treatment of chronic rather than acute conditions.* Drugs for acute conditions generally require more physician control of the dosage than that provided by sustained-release products.

The most common mechanisms utilized in rate-controlled pharmaceutical products are: solvent action of biologic fluids on coated drug particles, osmotic systems controlled by the diffusion of biologic fluids through a polymer, erodible systems controlled by the erosion of a polymeric matrix, diffusion systems controlled by the diffusion of the drug through a polymeric membrane or monolithic matrix, and chemical reaction or interaction between the drug substance or its pharmaceutical barrier and site-specific biologic fluids. These mechanisms are utilized in the development of dosage forms and drug delivery systems for oral and other routes of administration.

Examples of the pharmaceutical technology utilized to achieve rate-controlled and sustained release solid dosage forms are described below.

COATED BEADS OR GRANULES OR MICROENCAPSULATED DRUG. In this method a solution of the drug substance in a non-aqueous solvent such as a mixture of acetone and alcohol is coated (by pan or air-suspension coating) onto small inert non-pareil seeds or beads made of a combination of sugar and starch. In instances in which the dose of the drug is large, the starting granules of material may be composed of the drug itself. Then with some of the beads or granules remaining uncoated and intended to provide the immediately released dose of drug when taken, coats of a lipid material like beeswax or a cellulosic material like ethylcellulose are applied to the remainder (about two-thirds to three-fourths) of the granules, with some granules receiving a few coats and others many coats. Then the beads or granules of different thicknesses of coatings are blended in the desired proportions to achieve the proper blend. The coating material may be colored with a dye material so that the beads of different coating thicknesses will be darker in color and distinguishable from those having fewer coats and being lighter in color. When properly blended, the granules may be placed in capsules or tableted. The variation in the thickness of the coats and in the type of material used in the coating is reflected in the rate at which the body fluids are capable of penetrating the coating and in dissolving the drug. Naturally, the thicker the coat, the more resistant to penetration and the more delayed will be the drug release. The presence of drug granules of various coating thicknesses therefore produces the sustained drug release. The time-blood level profile is similar to that obtained with multiple dosing. An example of this type of dosage form is the *Spansule* capsule, shown in Figure 5–60.

Microencapsulation is a process by which solids, liquids, or even gases may be encapsulated into microscopic size particles through the formation of thin coatings of "wall" material around the substance being encapsulated. The process had its early origin in the late 1930s as a "clean" substitute for carbon paper and carbon ribbons as sought by the business machines industry. The ultimate development in the 1950s of reproduction paper and ribbons which contained dyes in tiny gelatin capsules released upon impact by a typewriter key or the pressure of a pen or pencil was the stimulus for the development of a host of microencapsulated materials, including drugs. Gelatin is a common wall-forming material but synthetic polymers as polyvinyl alcohol, ethylcellulose, or polyvinyl chloride have been used. The typical encapsulation process usually begins with the dissolving of the prospective wall material, say gelatin, in water. The material to be encapsulated is added and the two-phase mixture thoroughly stirred. With the material to

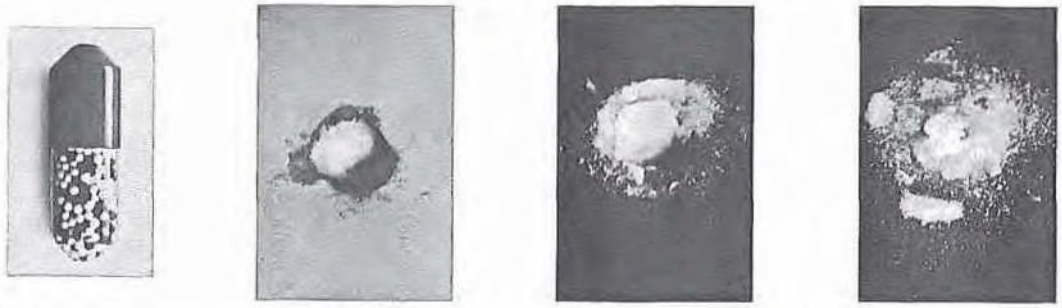

Fig. 5–60. *The* Spansule *capsule showing the hard gelatin capsule containing hundreds of tiny pellets for sustained drug release and the rupturing of one of the pellets as occurs in the gastric fluid. (Courtesy of SmithKline Beecham.)*

be encapsulated broken up to the desired particle size, a solution of a second material is added, usually acacia. This additive material is chosen to have the ability to concentrate the gelatin (polymer) into tiny liquid droplets. These droplets (coacervate) then form a film or coat around the particles of the substance to be encapsulated as a consequence of the extremely low interfacial tension of the residual water or solvent in the wall material so that a continuous, tight, film coating remains on the particle (Fig. 5–61). The final dry microcapsules are free-flowing, discrete particles of coated material. Of the total particle weight, the wall material usually represents between 2 and 20%. By varying the wall thickness of microencapsulated drug particles, their dissolution rates may be altered and sustained release obtained. An example of a drug commercially available in microencapsulated dosage form is potassium chloride as Micro-K (A. H. Robins).

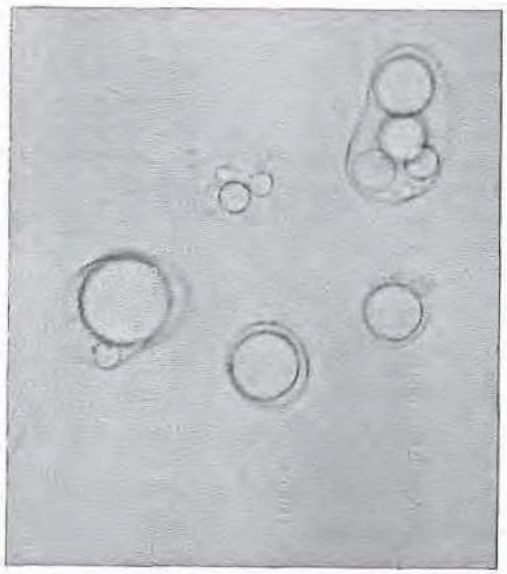

Fig. 5–61. *Microcapsules of mineral oil in a gelatin-acacia coacervate. (Photo courtesy of James C. Price, Ph.D., College of Pharmacy, The University of Georgia.)*

EMBEDDING DRUG IN SLOWLY ERODING MATRIX. By this process, the portion of the drug intended to have sustained action is combined with lipid or cellulosic material processed into granules that can be placed into capsules or tableted. When these granules are combined with granules of drug prepared without the special lipid or cellulosic excipient, the untreated portion provides the immediate drug effect, and the treated portion the prolonged effect. The treated granules slowly erode in the body fluids. The types of materials used in the preparation of the granules may be varied to achieve different rates of erosion. The product SLOW-K (Summit) is a sugar-coated tablet containing 8 mEq of potassium chloride in a wax matrix. The formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high (and irritating) localized concentrations of potassium within the gastrointestinal tract.

Two-layered tablets may be prepared from the granules, with one layer containing the untreated drug for immediate release and the other layer having the drug for sustained release. Three-layered tablets may be similarly prepared, with both outer layers containing the drug for immediate release. Some commercial tablets are prepared with an inner core containing the sustained release portion of drug and an outer shell completely enclosing the core and containing the drug portion for immediate release. Tablets prepared from the type of material described in the next method may be similarl

EMBEDDING DRUG IN INERT PLASTIC MATRIX. By this method, the drug is granulated with an inert plastic material such as polyethylene, polyvinyl acetate, or polymethacrylate, and the granulation is compressed into tablets. The drug is slowly released from the inert plastic matrix by leaching to the body fluids. The compression of the tablet creates the matrix or plastic form that retains its shape during the leaching of the drug and through its elimination from the alimentary tract. The initially released drug is present on the surfaces of the tablet or is only superficially embedded. The primary example of a dosage form of this type is the *Gradumet* (Abbott).

COMPLEX FORMATION. Certain drug substances when chemically combined with certain other chemical agents form chemical complexes that may be only slowly soluble in body fluids, depending upon the pH of the environment. This slow dissolution rate is effective to provide the sustained action of the drug.

It should be remembered that certain drug substances that are only slowly soluble in body fluids without special complexation or other treatment are inherently long acting.

ION-EXCHANGE RESINS. A solution of the cationic drug is passed through a column containing the ion-exchange resin, to which it complexes by the replacement of hydrogen atoms. The resin-drug complex is then washed and may be tableted, encapsulated, or suspended in an aqueous vehicle. The release of the drug is dependent upon the pH and the electrolyte concentration in the gastrointestinal tract. Generally, release is greater in the acidity of the stomach than the less acidic small intestine. Examples of drug products of this type include *Tussionex* suspension (hydrocodone polistirex) and *Ionamin* capsules (phentermine resin) both by Fisons.

The mechanism of action of drug release from ion exchange resins may be depicted as follows.

In the stomach:

(1) Drug resinate + HCl⇌acidic resin + drug hydrochloride
(2) Resin salt + HCl⇌resin chloride + acidic drug

In the intestine:

(1) Drug resinate + NaCl⇌sodium resinate + drug hydrochloride
(2) Resin salt + NaCl⇌resin chloride + sodium salt of drug.

This system incorporates a polymer barrier coating and bead technology in addition to the ion-exchange mechanism. The initial dose comes from an uncoated portion, and the remainder from the coated beads. The coating does not dissolve, and release is controlled over a 12-hour period by ionic exchange. The drug-containing polymer particles are minute, and may be suspended to produce a liquid with controlled-release characteristics [e.g., Tussionex (Fisons)] as well as solid dosage forms.

HYDROCOLLOID SYSTEM. Hydrocolloids can play a significant role in the design of a controlled-release product. An example is the product Valrelease, a 15-mg slow-release dosage form of Valium (diazepam/Roche). Valrelease has been formulated using a unique Hydro-dynamically Balanced drug-delivery System (HBS). This dosage form was designed to achieve, in one administration, plasma concentrations of diazepam equivalent to those obtained with conventional Valium 5 mg tablets taken 3 times daily. The Hydrodynamically Balanced drug-delivery System consists of a matrix so designed that upon contact with gastric fluid, the dosage form demonstrates a bulk density of less than one and, thus, remains buoyant. Capsules and tables prepared to have this characteristic are sometimes referred to as "floating" capsules or tablets. When the Valrelease capsule shell dissolves, the outermost hydrocolloids come in contact with gastric fluid. They swell to form a boundary layer, which prevents immediate penetration of fluid into the formulation. The outer hydrocolloid boundary layer gradually erodes, with the subsequent formation of another "outer" boundary layer. This is a continuous process causing the gelatinous mass to constantly erode, while diazepam is gradually released through each layer as the fluid slowly penetrates the matrix. Valrelease remains in the stomach for a variable period of time, depending on individual physiologic characteristics. However, when Valrelease passes into the intestine, gradual release of the active drug and absorption continue.

OSMOTIC PUMP. The Oros system, developed by Alza, is an *o*ral *o*smotic pump composed of a core tablet and a semi-permeable coating with a 0.4 mm diameter hole for drug exit. The hole is produced by a laser beam and the product operates on the principle of osmotic pressure (Fig. 5–62A). The semi-permeable membrane permits water to enter from the patient's stomach into the core, dissolving the drug. The pressure that is built up forces or pumps the drug solution out of the delivery orifice (Fig. 5–63).

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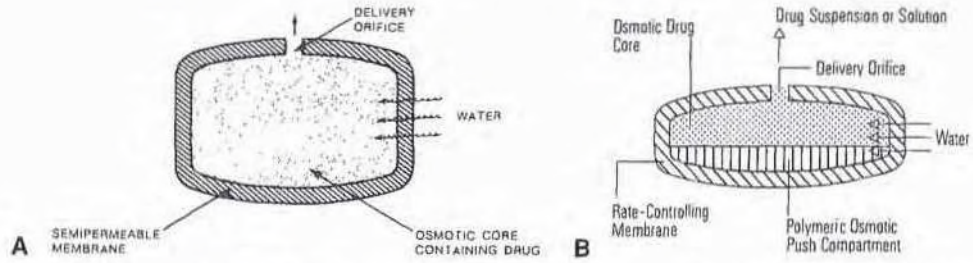

Fig. 5–62. *A, Depiction of the elementary OROS osmotic pump drug delivery system, and B, the OROS Push-Pull Osmotic System. (Courtesy of Alza Corporation.)*

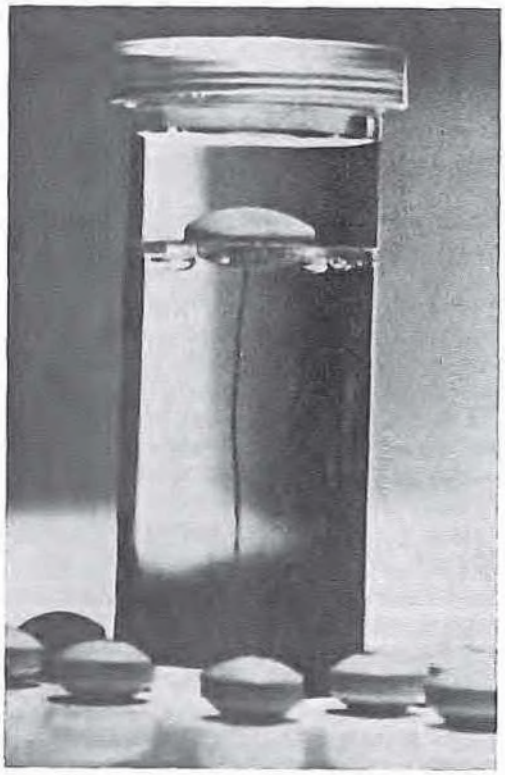

Fig. 5–63. *The OROS (Oral Osmotic) drug delivery system. A tablet core of drug is surrounded by a semipermeable membrane that is pierced by a small laser-drilled hole. After ingestion, water is drawn into the tablet from the digestive tract by osmosis. As water enters the tablet core, the drug gradually goes into solution. The solution is pushed out through the small hole at a controlled rate of about 1 to 2 drops per hour. (Courtesy of ALZA Corporation.)*

The rate of inflow of water and the outflow of drug solution are controlled by the properties of the membrane. Only the drug solution (not the undissolved drug) passes through the hole in the tablet. The rate of drug solution release is approximately one to two drops per hour. The drug-release rate is not affected by the acidity, alkalinity, or movement of the gastrointestinal tract. A currently marketed product of this type is Acutrim (CIBA Consumer).

Oros is a sophisticated oral controlled release drug delivery system in which the release rate may be controlled by changing the *surface area, the thickness* or *the nature* of the membrane and/or by changing the diameter of the drug release orifice.

The *OROS Push-Pull Osmotic System* has two layers (Fig. 5–62B) that are surrounded by a semi-permeable membrane. One layer contains the drug and the other contains a polymeric osmotic agent. When the tablet is swallowed, it draws in a few drops of water every hour across the membrane, slowly dissolving or suspending the drug, and expanding the polymeric osmotic compartment to release the drug through one or more laser-drilled holes at a controlled rate.

Other pharmaceutical companies have developed similar osmotic systems. For example, Elan Pharmaceutical has developed a system called Modas—*Multidirectional Osmotic Drug Absorption System.* Modas is an osmotic device with solubilized drug delivered through a fixed permeable membrane designed to admit moisture and excrete the soluble drug back through the same membrane at constant pressure. The drug comes out of the entire surface area of the tablet at a constant rate.

Repeat Action Forms

Some specialized tablets are prepared so that an initial dose of the drug is

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tablet shell and a second dose from an inner core of the tablet, which is separated from the outer shell by a slowly permeable barrier coating. Generally the barrier coating is penetrated and drug from the inner core is exposed to the body fluids some 4 to 6 hours after the swallowing of the tablet. Such a tablet permits the release of two doses of drug from a single tablet, eliminating the need for more frequent drug administration. An example of this type of dosage form is *Repetabs* (Schering). As for the sustained-action type of dosage forms, the repeat-action forms are best suited for those drugs having low dosage and employed in chronic conditions and for drugs having regular absorption patterns with fairly rapid rates of absorption and excretion.

Delayed Action Forms

The release of a drug from a dosage form may be intentionally delayed until it reaches the intestinal environment for any of several reasons. Among these may be the fact that the drug is destroyed by the gastric juices, or it may be excessively irritating to the lining of the stomach or a nauseating drug, or it may be better absorbed from the intestines than from the stomach. Capsules and tablets coated so as to remain intact in the stomach but yield their ingredients in the intestines are said to be *enteric coated*. The coating may be composed of a material that is pH dependent and breaks down in the less acidic environment of the intestine, or the coating may erode due to moisture and on a time basis coinciding with the time required for the tablet or capsule to reach the intestines. Other coatings may deteriorate due to the hydrolysis-catalyzing action of certain intestinal enzymes. Among the many agents used to enteric coat tablets and capsules are fats, fatty acids, waxes and mixtures of these, shellac, and cellulose acetate phthalate. An example of a commercially prepared brand of enteric coated tablets is *Enseals* (Lilly). A popular enteric-coated aspirin tablet is Ecotrin (SmithKline Beecham Consumer Brands).

Liposomes

In the early 1960s, research scientists noted that various phospholipids formed multilayered vesicles (sacs) when dispersed in water. These cell-like structures become known as *liposomes*. Like a biologic cell, a liposome is composed of a thin but durable membrane that surrounds an aqueous compartment, protecting it from the outside environment. Both cellular and liposome membranes are capable of regulating the transport of molecules in and out of the enclosed compartment. Thus liposomes may be used to control the passage of drugs, entrapped in the aqueous phase, through the membrane and to the intended body site for absorption or action. In recent years, drug-containing liposome systems have been developed for the delivery of drugs by various routes of administration including inhalation, ocular, injectable, dermal, and oral.

Liposomes may be constructed to have a single aqueous compartment surrounded by a lipid layer *(unilamellar)* or they may consist of concentric lipid and aqueous layers *(multilamellar)*. The structure of liposomes permits the incorporation of fat-soluble drugs in the lipid layer and water-soluble drugs in the interior aqueous compartment. Drugs encapsulated in the aqueous phase are released by slowly diffusing through the lipid membrane. Lipid-soluble drugs embedded in the lipid membrane or bound to the membrane surface are slowly released as the membrane is broken down by body fluids. Because lipids from natural sources are used to form the liposome membrane, liposomes are considered biocompatible and biodegradable.

Liposomes are produced by dispersing the lipid (usually phospholipids) phase in the drug solution. Simple mixing to vigorous agitation is applied to the system. Upon dispersion, the lipid molecules align to form the biomolecular membrane. The lipophilic ends of the lipid molecules intercalcate to form the inside of the membrane and the hydrophilic ends line up on the two outer surfaces. The membrane then wraps around, encapsulating the drug solution as the liposome is formed.

Generally, simple hand mixing of the phospholipid and aqueous phase produces a dispersion of multilamellar vesicles of large and widely mixed size. Various homogenizers and pressure flow-through devices have been utilized to achieve a more narrowly defined liposome size distribution. For use as drug carriers, liposomes should be homogeneous and reproducible in batch-to-batch production, stability, and drug release characteristics. Recently, microfluidization techniques have been used to produce liposomes of well-defined size distribution. This process involves the ultra high velocity interaction of two fluid streams in closely defined interaction. The pressures of the system, as high as 8000 psi, result in the jet interaction of the phases and lipo-

some formation rates of as high as 75%, in contrast to other mixing systems which may result in a capture of the aqueous phase between 8 to 25%.

Because of the variation in the method of preparation, the size of liposomes varies from about 0.3 to 10 microns. The size of liposomes influences both their distribution in the body and their deposition. For instance, following injection, large size liposomes can have the tendency to deposit in the lungs whereas smaller particles may concentrate in other body sites, such as the liver. Alterations in the membrane composition, the phospholipid configuration, or in the electrical charge on liposomes can also greatly influence their distribution in the body. Agents such as cholesterol and cetylphosphate have been incorporated into the phospholipid bilayers to alter the liposome's properties, changing not only the diffusion characteristics of the membrane but also the distribution of the liposome within the body following administration.

Several liposome products are under commercial development for inhalation, ocular, dermal and parenteral routes of administration. For example, liposome-based bronchodilators, delivered as nebulized and aerosolized solutions, are being designed to treat bronchospasm. Ocular delivery products containing "bioadhesive" liposomes that adhere to the eye's surface are being developed to provide lubricating eye drops and sustained effects for glaucoma medication. Liposome products for application of therapeutic agents to the skin and scalp to provide extended drug release and perhaps greater percutaneous absorption are being investigated. Liposome-based products are also being developed to target drugs to specific body organs following intravenous administration. The objective is to concentrate the drug's action at the desired body site to maximize therapeutic action and minimize toxicity. Drugs being studied include anticancer agents, antibiotics, and peptide hormones.

Other technologies for rate-controlled targeted delivery include the use of transdermal drug delivery systems, implantable (subcutaneous) drug delivery systems, ocular drug delivery systems, intravenous infusion pumps, and monoclonal antibodies which are utilized as specific carriers for drugs, enzymes, and radiopharmaceuticals in the diagnosis and treatment of disease. These technologies are discussed elsewhere in this text.

Pharmacist Monitoring of Patients Using Controlled-Release Drugs

When a patient is prescribed a controlled-release drug the attainment of the peak and therapeutic concentration of the drug might be somewhat delayed. If an immediate effect is desirable, either an intravenous dose or immediate-release dosage form of the drug would be preferable. Thus, a pharmacist when consulted about a dosing recommendation should keep this in mind as it relates to patient needs.

As mentioned earlier in this chapter variations in the bioavailability from a controlled-release product are possible so the pharmacist must be cognizant of patient complaints of unusual adverse effects or possible ineffectiveness. Therapeutic levels of the certain drugs, e.g., theophylline, must be maintained for the desired therapeutic outcome to occur and once a patient is stabilized on a controlled-release product it should not be substituted. A different product, even with an identical amount of active ingredient, could cause a marked shift in the patient's drug blood/serum level due to different release characteristics of the dosage form. Unless two controlled-release products of the same drug have demonstrated similar bioavailability and therapeutic effect they should not be used interchangeably or substituted for one another.

Packaging and Storing Tablets

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

In most instances of dispensing, the pharmacist is well advised to use a similar type of container as provided by the manufacturer of the product and the patient advised to maintain the drug in the container dispensed. Proper storage conditions as recommended for the particular drug should be maintained by the pharmacist and patient 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.[26]

Certain tablets containing volatile drugs, as nitroglycerin, may experience the migration of the drug between tablets in the container thereby resulting in a lack of uniformity among the tablets.[27] Further, packing materials, as cotton and rayon, in contact with nitroglycerin tablets may absorb varying amounts of nitroglycerin rendering the tablets sub-potent.[28]

In 1972, the Food and Drug Administration issued a number of regulations covering the packaging, labeling, and dispensing of nitroglycerin products. These regulations include:

1. All nitroglycerin tablets must be packaged in glass containers with tightly-fitting metal screw caps.
2. No more than 100 tablets may be packaged in each container.
3. Nitroglycerin tablets must be dispensed in their original containers and bear the label–"Warning: To prevent loss of potency, keep these tablets in the original container. Close tightly immediately after use."
4. All nitroglyercin tablets should be stored at controlled room temperatures of between 59° and 86°F.

Implementation of these regulations contributed to the maintenance of better content uniformity standards for nitroglycerin tablets than had been previously achieved. However, since nitroglycerin is a volatile liquid at room temperature, some nitroglycerin is lost to the atmosphere when the containers are opened and particularly if they are not tightly closed. In a further effort to reduce the loss of nitroglycerin from tablets and to prevent the migration of the substance from tablet to tablet, pharmaceutical manufacturers of these tablets have recently been developing "stabilized" nitroglycerin tablets. The main method used is to include a small amount of a nonvolatile substance in the formulation which has the effect of reducing the vapor pressure of the nitroglycerin and thus its tendency to escape from the tablet. One such marked product is *Nitrostat* by Parke-Davis which contains polyethylene glycol as the stabilizer.

Other Solid Dosage Forms for Oral Administration

Pills

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.

Lozenges

Lozenges are disc-shaped, solid dosage forms containing a medicinal agent and generally a flavoring substance and intended to be slowly dissolved in the oral cavity for localized effects. Lozenges are frequently called *troches* and less frequently referred to as *pastilles*. Many of the commercially available lozenges have a hard candy as the base or a base of sugar and an adhesive substance such as mucilage or gum.

Commercially, lozenges may be made by compression, 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 slowly dissolve or disintegrate in the mouth. Medicinal substances that are heat stable may be prepared 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 are gaining renewed acceptance as a means to deliver a multitude of different drugs. As an example, for the treatment of oropharyngeal candidiasis a lozenge dosage form is available with either nystatin or clotrimazole (e.g. Mycelex Troche, Miles) as its active ingredient. The patient allows the lozenge (or troche) to slowly dissolve in the mouth, and the dosage form is much more convenient to the patient when compared to the necessity of swishing an oral suspension in the mouth. Further, these lozenges maintain adequate salivary levels of the antifungal drug for about 3 hours and help to promote effectiveness of therapy. Lozenge dosage forms are also available for self-care drugs, e.g., benzocaine, dextromethorphan, phenylpropanolamine, to treat acute, self-limiting conditions ranging from minor sore throat to cough

and congestion. These forms are particularly advantageous for those persons who find it difficult to swallow solid dosage forms and for young children.

Proper Administration of Peroral Dosage Forms

The dosage forms discussed in this chapter are all to be administered by mouth. The easiest way is to place the dosage form upon the tongue and swallow it with a glassful of water. Most patients will understand this method of administration and do so with water. However, some persons do not realize that these dosage forms should be taken with water and may proceed to merely swallow the tablet or the capsule. This can be dangerous because it is possible for the tablet or capsule to lodge within the esophagus. Several documented cases of esophageal ulceration in young women, for example, have occurred with the ingestion of tetracycline and tetracycline derivatives, particularly when taken just before bedtime. Thus, it is important to counsel the patient to take all oral dosage forms with at least some water. This is particularly so with those dosage forms that contain aspirin, ferrous sulfate, any nonsteroidal antiinflammatory drug (NSAID), potassium chloride and any tetracycline drug, to ensure passage of the medicine into the stomach. It is equally important to also instruct patients to take these medications no later than at least 1 hour before retiring for the evening.

Senior citizens are at an increased risk because the process of swallowing medications like those mentioned takes longer, and if they have esophageal strictures, there is the potential for these to lodge in the esophagus. Further, patients who suffer from gastroesophageal reflux disease must also be cautioned to take medicines with water and at least 1 hour before retiring. Otherwise, there is a possibility that some of the medicine may be refluxed back into the esophagus from the stomach once the patient retires for the evening.

As mentioned earlier in this chapter, certain oral dosage forms have protective coatings, e.g., enteric-coated, or may be formulated to provide delayed or continuous release of the active ingredient. The patient must be advised not to chew or crush these tablets as the amount and the rate of release of the drug may be dramatically altered. The patient should also be forewarned that they may notice remnants of these types of dosage forms in the stool. They should be told not to be concerned as the drug portion of the preparation has already been absorbed.

When a tablet can be crushed or a capsule opened to facilitate oral administration the pharmacist must keep in mind that medicines usually have an unpleasant taste. The bitter taste of the drug could be masked partially by recommending to the patient to mix the drug with applesauce, fruit juice, or carbonated beverages. However, the patient must be advised to consume the entire mixture. Otherwise the patient will not receive the total dose.

For those who experience gagging or choking when taking a solid dosage form, there is an innovative product called the Drink-A-Pill Drinking Glass. This contains a specially-designed shelf on which a tablet or capsule is placed after the glass is filled with water. When the patient drinks the content of the glass, the dosage form flows with the water into the mouth and goes right down without the gag reflex. Alternatively, if the patient simply cannot swallow the solid dosage form, the pharmacist can suggest to the prescribing physician a liquid form of the drug. If such a preparation is not available, it may be possible to extemporaneously compound the drug into a liquid vehicle. Several liquid formulations from solid dosage forms are listed in the *Handbook on Extemporaneous Formulations*. If this is not possible, the pharmacist could recommend the use of an available liquid dosage form of a different chemical compound with similar therapeutic effect.

Solid Dosage Forms for Nonoral Route of Administration

There are a few solid dosage forms which are used by routes of administration other than oral. For instance, dosage forms called *pellets* or *inserts* are implanted under the skin by special injectors or by surgical incision for the purpose of providing for the continuous release of medication. Such implants provide the patient with an economical means of obtaining long-lasting effects and obviate the need for frequent injections or oral dosage administration. Hormonal substances are most frequently administered in this manner. For example, the Norplant® system (Wyeth-Ayerst) of levonorgestrel implants provides up to five years of protection from pregnancy after subcutaneous insertion. The implants are closed capsules made of a di-

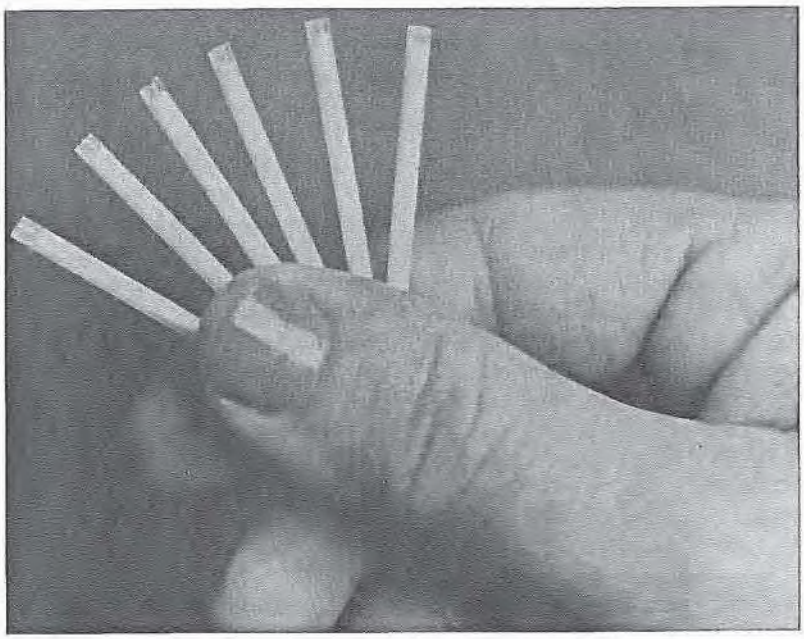

Fig. 5–64. *Norplant® System of levonorgestrel implants for the long-term (up to 5 years) prevention of pregnancy. Six implants are inserted subdermally in the midportion of the inner upper arm about 8 to 10 cm above the elbow crease. The implants are inserted in a fanlike pattern about 15 degrees apart. (Courtesy of Wyeth-Ayerst Laboratories.)*

methylsiloxane/methylvinylsiloxane copolymer containing 36 mg of the synthetic progestin levonorgestrel (Fig. 5–64). Each capsule is 2.4 mm in diameter and 34 mm in length. Six capsules are inserted in a plane beneath the skin of the upper arm by small incision and special injector. Following their term of use, the capsules are removed and may be replaced with fresh capsules.[29]

Other solid dosage forms, *vaginal tablets* or *inserts*, are specially formulated and shaped tablets intended to be placed in the vagina by special applicators, where the medication is released, generally for localized effects. Another example of a solid dosage form intended for use by means other than swallowing is a specially prepared capsule containing a micronized powder [Intal (Fisons)] intended to be released from the capsule and inhaled deep into the lungs through the use of a special inhaler-device (Spinhaler turboinhaler). These dosage forms and drug delivery systems will be discussed in subsequent chapters.

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