The Theory and Practice of Industrial Pharmacy

LEON LACHMAN, Ph.D.
Lachman Consultant Services, Inc.
Garden City, New York

HERBERT A. LIEBERMAN, Ph.D.
H. H. Lieberman Associates, Inc.
Consultant Services
Livingston, New Jersey

JOSEPH L. KANIG, Ph.D.
Kanig Consulting and Research Associates, Inc.
Ridgefield, Connecticut

THIRD EDITION

LEA & FEBIGER · 1986 · PHILADELPHIA

Lea & Febiger
600 Washington Square
Philadelphia, PA 19106-4198
U.S.A.
(215) 922-1330

Library of Congress Cataloging in Publication Data
Main entry under title:

The Theory and practice of industrial pharmacy.

Includes bibliographies and index.
1. Pharmacy. 2. Drug trade. I. Lachman, Leon, 1929– . II. Lieberman, Herbert A., 1920–
III. Kanig, Joseph L., 1921– [DNLM: 1. Drug Industry.
QV 704 T396]
RS192.L33 1985 615'.19 84-27806
ISBN 0-8121-0977-5

First Edition, 1970
Second Edition, 1976

PRINTED IN THE UNITED STATES OF AMERICA

Print No. 4 3 2 1

Contents

*Deceased.

3

Drying

ALBERT S. RANKELL, HERBERT A. LIEBERMAN,
and ROBERT F. SCHIFFMANN

There is hardly a pharmaceutical plant engaged in the manufacture of tablets or capsules that does not contain dryers. Unfortunately, the operation of drying is so taken for granted that efforts for achieving increased efficiency in the production of tablets do not include a study of drying. This chapter introduces the industrial pharmacist to the theory and fundamental concepts of drying.

Definition. For the purpose of this discussion, drying is defined as the removal of a liquid from a material by the application of heat, and is accomplished by the transfer of a liquid from a surface into an unsaturated vapor phase. This definition applies to the removal of a small amount of water from moisture-bearing table salt as well as to the recovery of salt from the sea by evaporation. Drying and evaporation are distinguishable merely by the relative quantities of liquid removed from the solid.

There are, however, many nonthermal methods of drying, for example, the *expression* of a solid to remove liquid (the squeezing of a wetted sponge), the *extraction* of liquid from a solid by use of a solvent, the *adsorption* of water from a solvent by the use of desiccants (such as anhydrous calcium chloride), the *absorption* of moisture from gases by passage through a sulfuric acid column, and the *desiccation* of moisture from a solid by placing it in a sealed container with a moisture-removing material (silica gel in a bottle).

Purpose. Drying is most commonly used in pharmaceutical manufacturing as a unit process in the preparation of granules, which can be dispensed in bulk or converted into tablets or capsules. Another application is found in the processing of materials, e.g., the preparation of dried aluminum hydroxide, the spray drying of lactose, and the preparation of powdered extracts. Drying also can be used to reduce bulk and weight, thereby lowering the cost of transportation and storage. Other uses include aiding in the preservation of animal and vegetable drugs by minimizing mold and bacterial growth in moisture-laden material and facilitating comminution by making the dried substance far more friable than the original, water-containing drug.

Dried products often are more stable than moist ones, as is the case in such diverse substances as effervescent salts, aspirin, hygroscopic powders, ascorbic acid, and penicillin. The drying reduces the chemical reactivity of the remaining water, which is expressed as a reduction in the water activity of the product. Various processes for the removal of moisture are used in the production of these materials. After the moisture is removed, the product is maintained at low water levels by the use of desiccants and/or low moisture transmission packaging materials. The proper application of drying techniques and moisture-protective packaging requires a knowledge of the theory of drying, with particular reference to the concept of equilibrium moisture content.

Psychrometry

A critical factor in drying operations is the vapor-carrying capacity of the air, nitrogen, or other gas stream passing over the drying material. This carrying capacity determines not only the rate of drying but also the extent of drying, i.e., the lowest moisture content to which a given material can be dried. The determination of the vapor concentration and carrying capacity of the gas is termed *psychrometry*. The air–water vapor system is the system most commonly employed in pharmaceutical drying operations and is therefore included in this discussion.

The concentration of water vapor in a gas is

called the *humidity* of the gas. Humidity may be expressed in various ways, depending on the information required. A knowledge of humidity is necessary, therefore, to understand the basic principles of drying.

Psychrometric Chart. The humidity characteristics of air are best shown graphically in a *psychrometric* or *humidity chart.* Such charts can be found in various handbooks.[1,2] The psychrometric chart has a formidable look because of the wealth of information presented in a small area. If the different curves in the chart are separated and analyzed individually, however, their utility and ease of use becomes apparent.

The basic curves of the psychrometric chart are shown in a simplified version in Figure 3-1. These curves are graphic representations of the relationship between the temperature and humidity of the air–water vapor system at constant pressure. The temperature is shown in the hori-

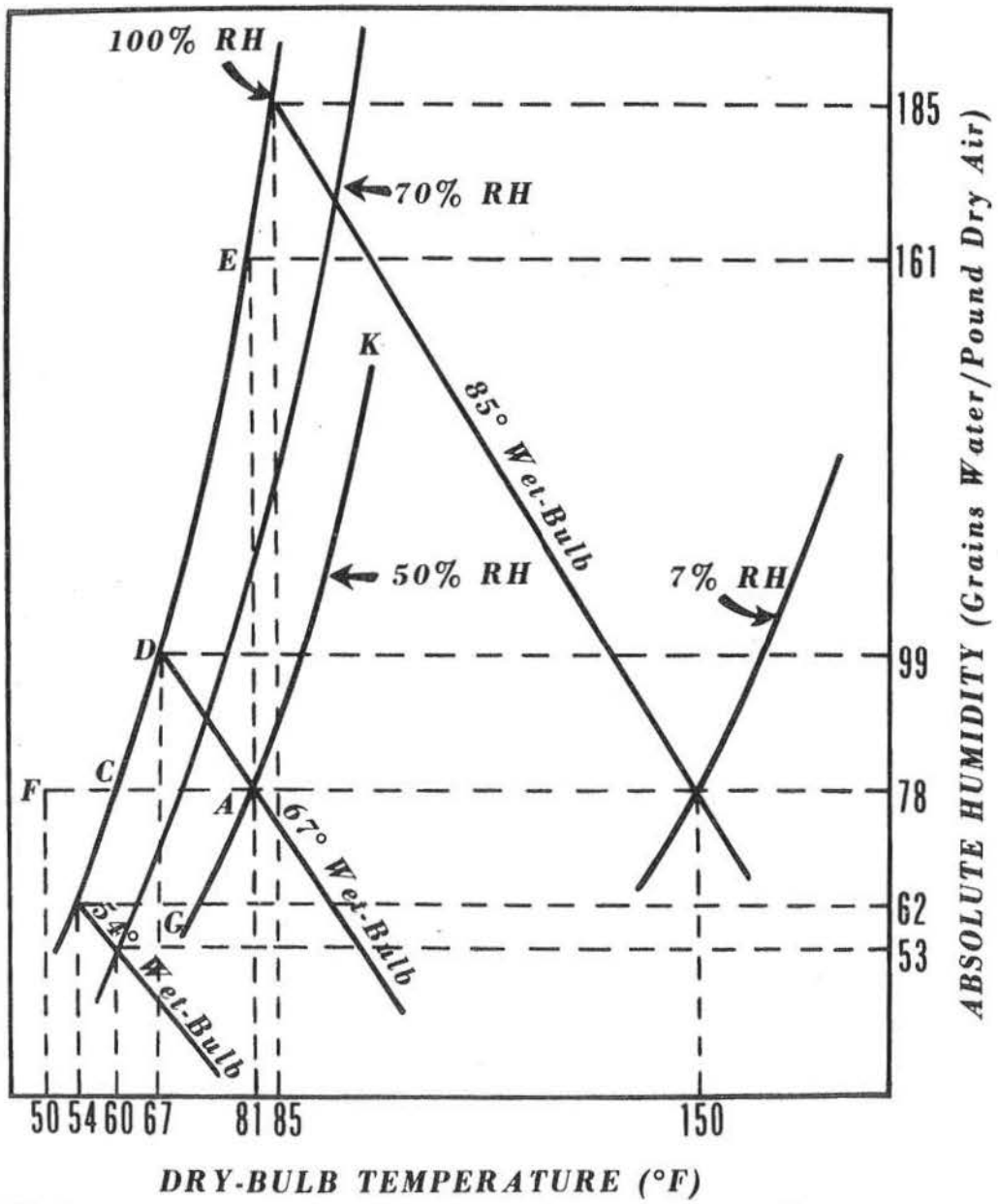

FIG. 3-1. *Diagram of psychrometric chart showing the relationship of air temperature to humidity.*

$$dW/d\theta = k'A(H_s - H_g) \quad (2)$$

where $dW/d\theta$ is the rate of diffusion expressed as pounds of water per hour; k' is the coefficient of mass transfer [pounds of water/(hour) (square foot) (absolute humidity difference)]; A is the area of the evaporating surface in square feet; H_s is the absolute humidity at the evaporating surface (pounds of water per pound of dry air); and H_g is the absolute humidity in the passing air stream (pounds of water per pound of dry air).

The coefficient of mass transfer, k', is not a constant, but varies with the velocity of the air stream passing over the evaporating surface. The relationship is in the form:

$$k' = cG^n \quad (3)$$

where c is a proportionality constant, G is the rate of flow of air [pounds of dry air/(hour) (square foot)], and n is a fractional exponent, usually about 0.8.[2]

After an initial period of adjustment, the rate of evaporation is equal to the rate of diffusion of vapor, and the rate of heat transfer [equation (1)] can be equated with the rate of mass transfer [equation (2)], or:

$$dW/d\theta = q/\lambda = k'A(H_s - H_g). \quad (4)$$

If the overall rate of heat transfer, q, is expressed as the sum of the rates of heat transfer by convection, radiation, and conduction, equation (4) is expanded to the form:

$$dW/d\theta = (q_c + q_r + q_k)/\lambda = k'A(H_s - H_g) \quad (5)$$

where q_c, q_r, and q_k are the rates of heat transfer by convection, radiation, and conduction, respectively.

The rate of drying may be accelerated by increasing any of the individual terms in equation (5). The rate of convection heat transfer, q_c, can be increased by increasing the air flow rate and by raising the inlet air temperature. The rate of radiation heat transfer, q_r, can be speeded up by introducing a high-temperature radiating heat source into the drying chamber. The rate of conduction heat transfer, q_k, can be stepped up by reducing the thickness of the material being dried and by allowing it to come in contact with raised-temperature surfaces. Increasing the air velocity also speeds up the rate of drying by increasing the coefficient of mass transfer, k', as shown in equation (3). Dehumidifying the inlet air, thus increasing the humidity differential, $(H_s - H_g)$, is still another means of speeding up the rate of drying.

Rapid drying may also be accomplished through the application of a microwave or dielectric field. In this case, heat is generated internally by the interaction of the applied electromagnetic field with the solvent. Mass transfer results from an internal pressure gradient established by the internal heat generation, while the mass concentration remains relatively uniform. The drying rate, then, primarily depends on the strength of the field applied to the material.

The utility of equation (5) in actual practice can be demonstrated by the following analysis: What is the effect of heating the air in a dryer to 150°F if the outside air is 81°F with 50% relative humidity? From the psychrometric chart (Fig. 3-1), it can be seen that for ambient air at this condition (point A), the absolute humidity is 78 grains water/pound dry air. Following the wet-bulb temperature line from this point to the saturation curve (point D) yields an absolute humidity of 99 grains water/pound dry air.

For the ambient air, the humidity differential $(H_s - H_g)$ is (99 − 78), which is equal to 21 grains (0.003 pounds) water/pound dry air. When this air is heated to 150°F, the absolute humidity remains the same, but the relative humidity is now reduced to 7%, and following the new wet-bulb temperature line (85°F) to the saturation curve yields a saturation humidity of 185 grains water/pound dry air. The humidity gradient is now 185 − 78, which is equal to 107 grains (0.0153 pounds) water/pound dry air, an increase of fivefold, indicating an increase in drying rate of 500% produced by a 69°F rise in temperature. In actual practice, the increase in drying rate would be even higher because increasing the inlet air temperature would increase k' as well as the humidity gradient. It should be noted that this increase in the drying rate does not produce a serious increase in the temperature of the material being dried, because the wet-bulb temperature of the 150°F air is only 85°F.

The foregoing discussion holds true as long as there is a film of moisture on the surface of the material being dried. When the surface becomes partially or completely dry, the heat and mass transfer equations become more complex. In this case, the rate of drying is controlled by the rate of diffusion of moisture from the interior of the material. This diffusion is greatly influenced by the molecular and capillary structure of the solid. The process becomes further complicated when the drying surface causes a shrinkage of

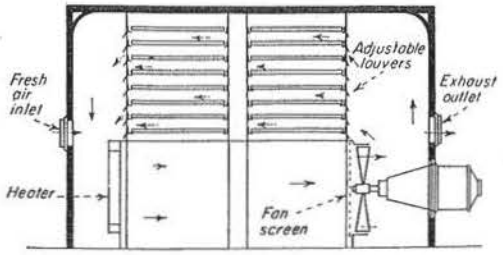

FIG. 3-6. *Tray dryer. (Courtesy of the Proctor and Schwartz Company.)*

formed in a moving belt dryer. Batch drying is used extensively in the manufacture of pharmaceuticals for several reasons: (1) Each batch of material can be handled as a separate entity. (2) The batch sizes of the pharmaceutical industry are relatively small (500 or less pounds per batch) compared with the chemical industry (2000 or more pounds per hour). (3) The same equipment is readily adjusted for use in drying a wide variety of materials.

Tray dryers may be classified as direct or indirect. Most tray dryers used in the pharmaceutical industry are of the direct type, in which heating is accomplished by the forced circulation of large volumes of heated air. Indirect tray dryers utilize heated shelves or radiant heat sources inside the drying chamber to evaporate the moisture, which is then removed by either a vacuum pump or a small amount of circulated gas. Further discussion in this section is confined to the direct (convection-type) dryer. Vacuum dryers are described separately later in the chapter.

The trays used have solid, perforated, or wire mesh bottoms. The circulation of drying air in trays with a solid base is limited to the top and bottom of the pan, whereas in trays with a perforated screen, the circulation can be controlled to pass through each tray and the solids on it. The screen trays used in most pharmaceutical drying operations are lined with paper, and the air thus circulates across rather than through the drying material. The paper is used as a disposable tray liner to reduce cleaning time and prevent product contamination.

To achieve uniform drying, there must be a constant temperature and a uniform airflow over the material being dried. This is accomplished in modern dryers by the use of a well-insulated cabinet with strategically placed fans and heating coils as integral parts of the unit. The air circulates through the dryer at 200 to 2000 feet per minute. The use of adjustable louvers helps to eliminate nonuniform airflow and stagnant pockets.

The preferred energy sources for heating the drying air used on pharmaceutical products are steam or electricity. Units fired with coal, oil, and gas produce higher temperatures at lower cost, but are avoided because of possible product contamination with fuel combustion products, and explosion hazards when flammable solvents are being evaporated. Steam is preferred over electricity, because steam energy is usually cheaper. If steam is not readily available, and drying loads are small, electric heat is used.

Tunnel and Conveyor Dryers. Tunnel dryers are adaptations of the truck dryer for continuous drying. The trucks are moved progressively through the drying tunnel by a moving chain. These trucks are loaded on one side of the dryer, allowed to reside in the heating chamber for a time sufficiently long to effect the desired drying, and then discharged at the exit. The operation may be more accurately described as *semicontinuous,* because each truck requires individual loading and unloading before and after the drying cycle. Heat is usually supplied by direct convection, but radiant energy also may be used.

Conveyor dryers are an improvement over tunnel dryers because they are truly *continuous.* The individual trucks of the tunnel are replaced with an endless belt or screen that carries the wet material through the drying tunnel. Conveyor dryers provide for uninterrupted loading and unloading and are thus more suitable for handling large volumes of materials.

The drying curve characteristic of the material in batch drying is altered considerably when continuous type dryers are used. As the mass is moved along its drying path in a continuous operation, this mass is subjected to drying air, the temperature and humidity of which are continually changing. As a consequence, the "constant rate" period is not constant, but decreases as the air temperature decreases, although the surface temperature of the wetted mass remains constant. Thus, drying rate curves for batch drying are not equally applicable to continuous drying procedures.

Moving-Bed Systems

Turbo-Tray Dryers. The turbo-tray dryer, illustrated in Figure 3-7, is a continuous shelf, moving-bed dryer. It consists of a series of rotating annular trays arranged in a vertical stack, all of which rotate slowly at 0.1 to 1.0 rpm. Heated air is circulated over the trays by turbo-type fans mounted in the center of the stack. Wet mass fed through the roof of the dryer is leveled by a stationary wiper. After about seven-eighths of a revolution, the material being dried is pushed

ployed: condensers, desiccants, and pumps. The water vapor is removed from the drying chamber and condensed in the form of a thin layer of ice on a heat-transfer surface in the condenser. The ice is removed intermittently by melting it with a heated fluid that is circulated through the condenser, or in the case of a continuous operation, by means of scraper blades. Liquid or solid desiccants are often employed in the initial vapor removal to enhance the efficiency of the pumps removing the water vapor. In general, scraper blades and desiccants are used for freeze drying large-volume biologicals (e.g., serum, penicillin), and usually are not used for preparing pharmaceutical dosage forms.

Microwave Drying. The application of microwave energy to the drying of solids represents a radical departure from conventional means of drying. Instead of applying heat externally to a material, energy in the form of microwaves is converted into internal heat by interaction with the material itself. This permits extremely rapid heat transfer throughout the material, which in turn can lead to rapid drying.

The heating effect is produced by the interaction of a rapidly oscillating electric field (915 or 2450 megahertz) with the polarized molecules and ions in the material. The field imposes order on otherwise randomly oriented molecules. As the field reverses polarity, it relaxes and allows the molecules to return to their random orientation, giving up stored potential energy as random kinetic energy, or heat. The interaction of the alternating field with ions causes billiard-ball-like collisions with un-ionized molecules, and the impact energy is converted into heat.

A given material's molecular and ionic makeup intimately affects its ability to be dried, as is shown in the power conversion equation for microwave heating:[9]

$$P = kfE^2\epsilon' \tan \delta = kfE^2\epsilon'' \quad (9)$$

where: P = the power developed, (watts/unit volume)
k = a constant
f = the frequency
E = the electric field strength, (volts/unit distance)
ϵ' = the relative dielectric constant of the material being heated
$\tan \delta$ = the loss tangent, or dissipation factor of the material
ϵ'' = the loss factor of the material, equal to the product $\epsilon' \tan \delta$

In microwave drying, the mass transfer is primarily the result of a pressure gradient due to rapid vapor generation inside the material, that is, most of the internal moisture is vaporized before leaving the sample. Thus, the moisture is mobilized as a vapor rather than a liquid, and its movement to the surface can be extremely rapid because it does not depend on mass concentration gradients or on slow liquid diffusion rates.

Industrial microwave dryers are usually of the static bed continuous type. Materials to be dried are placed on conveyor belts and conveyed through the microwave applicator. Generally, a stream of hot air is used simultaneously with the microwaves to sweep away the moisture evolving from the surface of the material being dried. Often, the microwave treatment is used in the last stages of hot air drying (the second falling rate period of Fig. 3-3) to remove the last remaining portion of the solvent, reducing total drying time by 50% or more.

Microwave drying can be used for the drying of pharmaceutical materials at low ambient temperatures, avoiding high surface temperatures, case hardening, and solute migration. Microwave vacuum drying at low pressure (1 to 20 mm Hg) and moderate temperature (30 to 40°C) can be used for drying thermolabile materials such as vitamins, enzymes, proteins, and flavors.

The rising cost of energy has generated a great deal of interest in microwave drying. The microwaves couple directly into the solvent, and no energy is used to heat the air, the walls of the dryer, the conveyor, or the trays. This results in extremely efficient energy utilization, and energy savings of as much as 70% have been realized in industrial installations.

References

1. Zimmerman, O. T., and Lavine, I.: Psychrometric Charts and Tables. Industrial Research Service, Dover, NH, 1945.
2. Perry, R. H., and Green, D. W.: Perry's Chemical Engineers' Handbook. 6th Ed. McGraw-Hill, New York, 1984.
3. Bone, D. P.: Food Prod. Devel., *3*:81, 1969.
4. Callahan, J. C., et al.: Drug Devel. and Industrial Pharmacy, *8*:355, 1982.
5. Rockland, L. B., and Nishi, S. K.: Food Technol., *34*:42, 1980.
6. Scott, M. W., et al.: J. Pharm Sci., *52*:284, 1963.
7. Kuelling, W., and Simon, E. J.: Pharm. Technol. Int., *3*:29, 1980.
8. Nuernberg, E.: Acta Pharm. Technol., *26*:39, 1980.
9. Lyons, D. W., and Hatcher, J. D.: J. Heat Mass Transfer, *15*:897, 1972.

6

Pharmaceutical Rheology

JOHN H. WOOD

Pharmaceutical fluid preparations are recognized as materials that pour and flow, having no ability to retain their original shape when not confined. The semisolids are a more nebulous grouping. They essentially retain their shape when unconfined but flow or deform when an external force is applied. Those materials that readily pour from bottles and form a puddle are clearly fluids. Ointments or pastes that clearly retain their shape after extrusion from a tube characteristically are associated with pharmaceutical semisolids. Obviously a continuum of properties exists between these limits.

Rheology (from the Greek *rheos* meaning flow and *logos* meaning science) is the study of the flow or deformation under stress. In pharmaceutical and allied research and technology, rheologic measurements are utilized to characterize the ease of pouring from a bottle, squeezing from a tube or other deformable container, maintaining product shape in a jar or after extrusion, rubbing the product onto and into the skin, and even pumping the product from mixing and storage to filling equipment. Of extreme importance in both product development and quality assurance is the determination that the desired attributes of body and flow are retained for the required shelf-life of the product.

Definitions and Fundamental Concepts

The tangential application of a force to a body and the resultant deformation of that body are the essential components for a rheologic observation. If this force is applied for only a short time and then withdrawn, the deformation is defined as *elastic* if the shape is restored, but as *flow* if the deformation remains. A *fluid* or *liquid* then becomes a body that flows under the action of an infinitesimal force. In practice, gravity is generally regarded as the criterion of such a minimal force.

To best understand the fundamental components of viscous flow, consider Figure 6-1. Two parallel planes are a distance x apart; between the planes, the viscous body is confined. The top, plane A, moves horizontally with velocity v because of the action of force F. The lower plane B is motionless. As a consequence, there exists a velocity gradient v/x between the planes. This gradient is given the definition of *rate of shear,* D. The *shear stress,* S, is the force per unit area creating the deformation.

Example 1. If some oil is rubbed into the skin with a relative rate of motion between the two surfaces of 15 cm/sec, and the film thickness is 0.01 cm, then the shear rate is as follows:

$$D = \frac{15}{0.01}\frac{\text{cm/sec}}{\text{cm}}$$
$$= 1500\ \text{sec}^{-1}$$

This shear stress may be applied either momentarily or continuously. Elastic deformation occurs if, as the force is applied, the upper plate moves in the direction of the force only momentarily and then stops but returns to its original position when the deforming force is removed. On the other hand, pure viscous flow occurs if there is continuous movement during the applied force, and no restorative motion follows removal of the deforming force.

Between the limits of elastic deformation and pure viscous flow, there exists a continuum of combinations of these limits. Such behavior is called *viscoelastic flow.* The elastic component of viscosity is considered in a later section.

Newtonian fluid is a fluid in which a direct

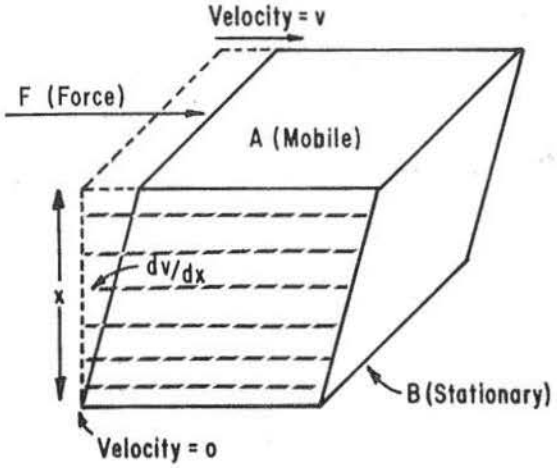

FIG. 6-1. *Model to demonstrate components of classic viscous flow.*

proportionality exists, for all values of shear, between shear stress and shear rate.

Viscosity or *coefficient of viscosity* is the proportionality constant between shear rate and shear stress. Conventionally, viscosity is represented by η. Then:

$$\eta = S/D \qquad (1)$$

The centimeter-gram-second (C.G.S.) system uses grams per centimeter per second ($g\ cm^{-1}\ sec^{-1}$) as the dimensional units of viscosity. In these units, viscosity is expressed in *poises*, a term used in recognition of the pioneering work in the 1840s of the French scientist J. L. M. Poiseuille. For dilute aqueous solutions, the common unit becomes the centipoise (10^{-2} poise), cp. The viscosity of water is about 1 cp.

In the newly adopted International System of Units (SI), the unit corresponding to the centipoise is the millipascal-second (mPas).

A perspective of these units may be obtained by considering the case of Figure 6-1 when a force of 1 dyne acts to produce a velocity of 1 cm/sec for plate A when the distance between plates is 1 cm, and both plates are 1 cm^2 in cross-sectional area. Under these terms, viscosity is calculated as:

$$\eta = \frac{S}{D}$$

$$= \frac{\text{force/area}}{\text{velocity difference/distance}}$$

$$= \frac{\text{dyne/cm}^2}{\text{(cm/sec)/cm}}$$

$$= \text{dyne sec cm}^{-2}$$

However, the dyne is the force acting for 1 sec to produce a velocity in a 1-g mass of 1 cm/sec. Hence, this dimensional analysis for viscosity reduces to:

$$\eta = g \cdot cm^{-1}\ sec^{-1}$$
$$= \text{poise}$$

In the International System of Units, which is not yet used routinely in viscosity references, the pascal (Pa) is the unit of stress and has the dimensions of newton/meter^2, where the newton is a kilogram meter/second^2. Hence, equivalence occurs for the centipoise with millipascal-seconds.

Example 2. If in example 1, the oil had the same viscosity as water, then the force used to create the shear can be determined as follows:

$$\eta = \frac{S}{D}$$

$$1 \times 10^{-2}\ \text{poise} = \frac{S}{1500}\ sec^{-1}$$

$$\text{Then } S = (1500)(1 \times 10^{-2})(sec^{-1})(\text{poise})$$
$$= 15\ (sec^{1})(\text{dyne sec cm}^{-2})$$
$$= 15\ \text{dyne cm}^{-2}$$

Example 3. In S.I. units, the above terms would become:

$$\eta = 1\ \text{mPas}$$
$$D = 1500\ sec^{-1}$$
$$S = 1.5\ \text{Pa}$$

Fluidity is the reciprocal of the viscosity, usually designated by the symbol ϕ. This is an occasional unit of convenience but not an essential one.

Kinematic viscosity (ν) is the Newtonian viscosity divided by density (η/d). The unit is now the *stoke*, in honor of the English scientist who studied problems of gravitational settlement in fluids. As discussed later in this chapter, certain fluid flow viscometers give values in this kinematic scale.

Example 4. If the oil from examples 1 and 2 had a density of 0.82, then the kinematic viscosity would be:

$$\nu = \frac{\eta}{d}$$

$$= \frac{1 \times 10^{-2}}{0.82}$$

$$= 1.22 \times 10^{-2}\ \text{stokes}$$
$$= 1.22\ \text{centistokes}$$

Non-newtonian fluids are those in which there is no direct linear relationship between shear stress and shear rate. Most systems of pharmaceutical interest fall into this category. The shear stress necessary to achieve a given shear rate may increase more rapidly or less rapidly than is required by the linear direct proportionality (Fig. 6-2).

A *pseudoplastic* material is one in which the stress increases at less than a linear rate with increasing shear rate, while a *dilatant* material is one in which the increase is more rapid. Thus, if viscosity is calculated at each of a series of shear rate points by use of equation (1), then the resultant values *decrease* with increasing shear rate for pseudoplastic materials and *increase* for dilatant ones. Measurements at such single points are frequently referred to as *apparent viscosity* to recognize clearly that the number quoted refers only to the condition of measurement. Although frequently, reference is carelessly made to a lotion having a viscosity of 300 cp or to a paste or ointment having a viscosity of 1200 poises, these are meaningless terms unless the shear rate at which the measurement was made becomes a clear part of the statement. The fact that one number cannot characterize the viscous behavior, however, requires the use of some equation of state. One such empiric one is the Power Law Equation:

$$S = A\,D^n \qquad (2)$$

where S and D are the shear stress and shear rate respectively, A is an appropriate proportionality constant, and n is the Power Index. In this form, n is less than 1 for pseudoplastic materials and greater than 1 for dilatant materials. The Power Law Equation is also used with the index n associated with stress rather than shear rate. Obviously, the magnitude of the values of n are then interchanged. Unfortunately, there is no clear convention for such equations.

When the logarithm of both sides of equation (2) is taken, the result is:

$$\log S = \log A + n \log D \qquad (3)$$

Compared with the equation of a straight line, $y = b + mx$, a plot of log S against log D results in a straight line of slope n and intercept log A. Figure 6-3 shows such plots on logarithmic scale for one gum system as a function of gum concentration.

Example 5. Calculate the parameters of the Power Law Equation for 0.01%, 0.02%, 0.04%, and 0.10% gum solutions. The following data apply to this case.

Composition	*Stress at D = 1*	*Stress at D = 10*
.01%	0.35 dyne cm^2	2.1 dyne cm^2
.02	6.2	20
.04	61	132
.10	205	440

The slope of each line is obtained from:

$$n = \frac{\log S_{(D=10)} - \log S_{(D=1)}}{\log 10 - \log 1}$$

$$= \frac{\log (S_{10}/S_1)}{1 - 0}$$

$$= \log \frac{S_{10}}{S_1}$$

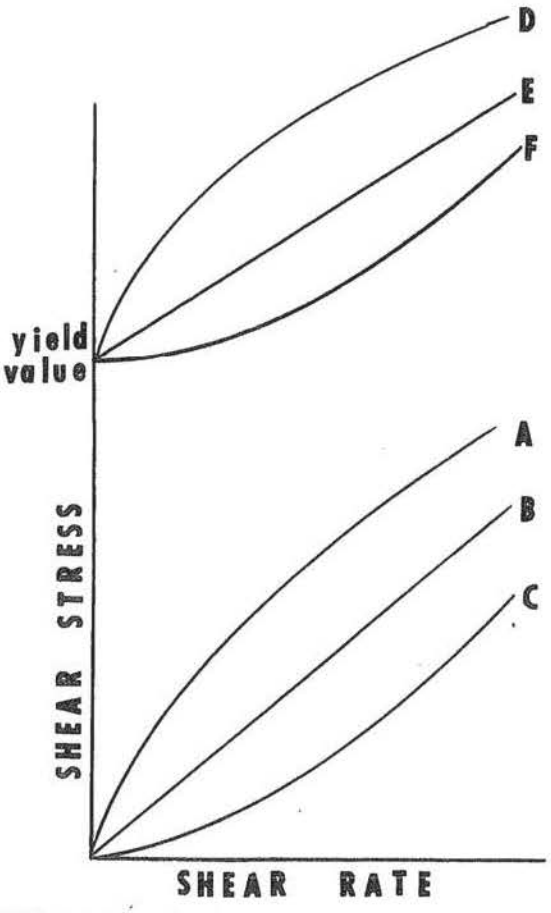

FIG. 6-2. *Examples of basic types of rheograms. A, Pseudoplastic or power law; B, Newtonian; C, dilatant; D, pseudoplastic with yield value; E, Bingham or Newtonian with yield value; F, dilatant with yield value.*

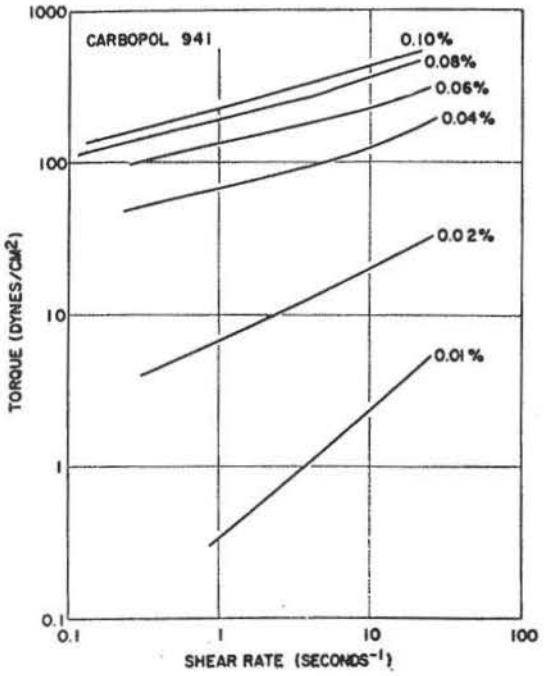

FIG. 6-3. *Logarithmic plots of the rheograms of Carbopol 941. (From Catacalos, G., and Wood, J. H.: J. Pharm. Sci., 53:1089, 1964. Reproduced with permission of the copyright owner, the American Pharmaceutical Association.)*

The slopes are then $\log \frac{2.1}{0.35}$, $\log \frac{20}{6.2}$, $\log \frac{132}{61}$, and $\log \frac{440}{205}$ for the four successive concentrations. These reduce to 0.78, 0.51, 0.34, and 0.33 respectively.

The intercept of a line is the value of y for $x = 0$, or here the value of log S for (log D) = 0, but the logarithm is zero when the number is unity, $\log 1 = 0$. Therefore, the intercepts of the four concentrations are log 0.35, log 6.2, log 61, and log 205. Numerically then, these values of log S are the values log A. Hence, the values of A are 0.35, 6.2, 61, and 205 respectively. The Power Law Equations are then:

0.01%	$S = 0.35D^{0.78}$
0.02	$S = 6.2D^{0.51}$
0.04	$S = 61D^{0.34}$
0.10	$S = 205D^{0.33}$

When an initial finite force is necessary before any rheologic flow can start, this initial stress is called *yield value.* A *Bingham plastic* is represented by a straight line or curve on the stress-shear rate plot being displaced from the origin by a finite stress value, the yield value. Thus, for Newtonian behavior at stresses (S) greater than the yield value (f) we have:

$$S - f = UD \qquad (4)$$

where U is the plastic viscosity and D is the shear rate. Similarly (see Fig. 6-2), both pseudoplastic and dilatant curves may appear to exhibit yield value. The dimensional units of the yield value must be those of the shear stress.

Because of the variety of parameters involved, no single measurement can characterize a non-Newtonian system. This can be seen in Figure 6-4. A wide variety of curves can pass through any specific value of shear stress and shear rate, exemplified here by the common focus of pseudoplastic, dilatant, and Newtonian lines. At the focal point, all have the same apparent viscosity, but at no other point do they have related values.

Properties Contributing to Rheologic Behavior

In general, Newtonian liquids are either pure chemicals or solutions of lower molecular weight compounds rather than of polymeric materials. All interactions are such that no structure is contributed to the liquid. Since by definition, shear stress and shear rate are directly proportional, a single viscometric point can characterize the liquid rheology. Increasing temperature decreases viscosity as it reduces intramolecular forces of attraction. Such temperature viscosity relationships are quickly established, regardless of whether temperature is increased or decreased.

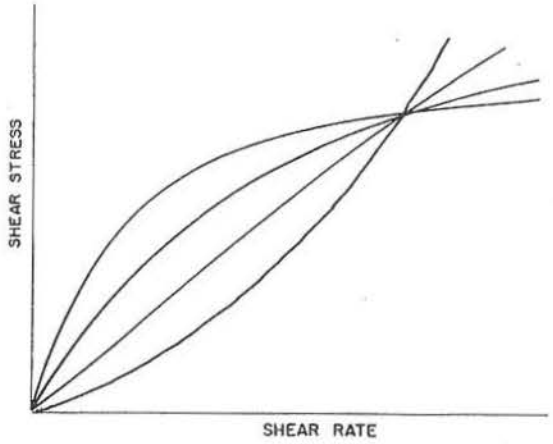

FIG. 6-4. *Different rheograms all have the same apparent viscosity at the common foci but not at any other point.*

Pseudoplastic behavior is exhibited by polymer solutions and by most semisolid systems containing some polymer components. In such systems, there is a buildup of interlacing molecular interactions. Long straight-chain polymers tend to have some coiling in their condition of minimum energy. These coils can develop a degree of interlocking. With branched polymers, the opportunity for frictional interlock is obviously even greater. In addition or alternatively, intramolecular bridging may occur by simple hydrogen bonding. This bonding may create innumerable bridges between individual adjacent molecules to create a complete cross-linking. As an example, water added to a liquid nonionic in the correct ratio can create a solid gel. In the case of silica or alumina gel, water may serve alone or with other agents from cross-linking to create a three-dimensional polymer structure. Classically, most suspending agents exhibit similar capability for development of structure. Depending on the nature of the suspending and cross-linking materials used, these adjuvants may or may not be in complete homogenous solution. Instead, these agents may have a strong affinity for the solvent and yet be partially insoluble. In systems with dispersed solids, these colloid solutions can serve as the interweaving material to hold the whole system together.

When shear is slowly imparted to such a system, deformation may initially occur with some difficulty, but once initiated, it becomes progressively easier as successive increments of force are applied. The nature of the interlocking or interwoven structure dictates whether initial flow occurs with difficulty until sufficient structure is lost or whether a sufficient initial force is required to initiate motion, that is, whether a *yield value* has to be exceeded. In any case, continued shearing breaks further linkages, so that the apparent viscosity drops with increasing shear. As shear stress is then decreased, the structure may or may not recover immediately. If recovery occurs rapidly, the ascending and descending shear-stress/shear-rate rheograms will be essentially superimposable. If the structure does not immediately recover, the descending rheogram will have lower stress values at each shear rate than the ascending (Figure 6-5). Such a body is said to be *thixotropic* and the loop, a *hysteresis* loop, is in area a measure of the thixotropy.

Occasionally, semisolid systems in shear, particularly those containing an appreciable solid content or those in which structure is developed through a three-dimensional polymer (silicate system), develop shear planes across which virtually no interactions exist, and hence, flow is easy. These planes of slippage result in what is called *plug flow*. In such a system, one portion moves with the shear stress, while the residue remains at rest. As is discussed later, this results in confusing rheologic implications for product performance. In general, such measurements are less reproducible.

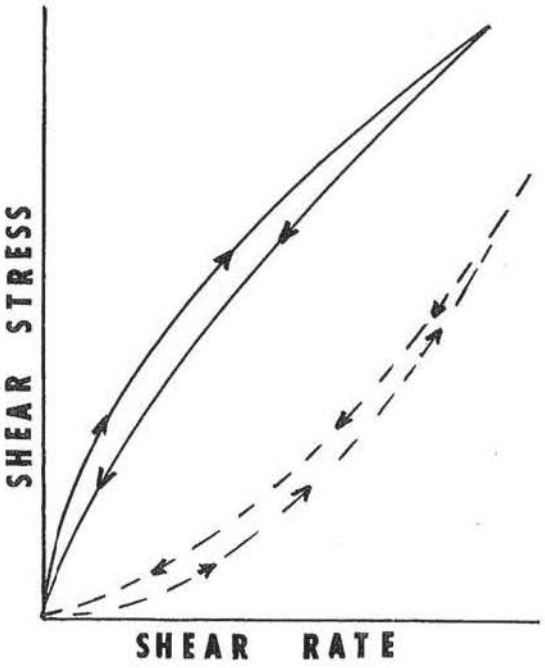

FIG. 6-5. *The solid lines represent ascending and descending rheograms for a pseudoplastic system exhibiting thixotropy. The dashed lines represent a dilatant system with a loop of rheopexy.*

Classic rheology cannot handle time-dependent phenomena except to display changes in stress under continuing shear. Thixotropy is therefore a phenomenon resulting from the time dependency of the breakdown or the rebuilding of structure. It is an empiric observation of good reliability that structure breakdown or buildup is an exponential function of time. Thus, if the observed shear stress for a given shear rate is followed with time, a plot of stress against time, both on the logarithmic scale, results in a straight line. Green and Weltmann used a variant of this observation to derive a coefficient of thixotropic breakdown (B) by the equation:[1]

$$B = \frac{S_1 - S_2}{\ln(t_2/t_1)} \qquad (5)$$

where S_1 and S_2 are the stress values at times t_1 and t_2 of continuous shear at any arbitrary shear

12

Tablet Coating

JAMES A. SEITZ, SHASHI P. MEHTA, *and* JAMES L. YEAGER

Historical Perspective

No discussion on tablet coating would be complete without a brief historical review of pharmaceutical coating to provide an appropriate perspective to the evolutions in the coating process that have occurred over the past thousand years.

One of the earliest references to coated solid dosage forms appears in early Islamic drug literature, where coated pills were mentioned by Rhazes (850–923).[1] The use of coating on drugs was probably an adaptation from early food preservation methods, and French publications in the 1600s described coating as a means of masking the taste of medicines. Sugar coating of pills was developed to a considerable extent by the French in the mid-1800s, and patents issued in 1837 and 1840 utilized sugar compositions for coated pills of cubeb and copaiba. Subsequently, there was rapid acceptance of sugar-coated pills as the preferred solid dosage form for both prescription and patent medicines in Europe and the United States. It soon was recognized that quality sugar coating on a large scale could be accomplished more readily in coating pans, and several early pharmaceutical companies in the United States were established, with coated pills as a major part of their product line.

Except for the substitution of compressed tablets for pills, the sugar coating equipment and process remained essentially unchanged for the next 75 years. In 1953, a dramatic change was made in tablet coating when Abbott Laboratories marketed the first film-coated pharmaceutical tablet. Concurrently, in the early 1950s, Dr. Dale Wurster, a professor at the University of Wisconsin, patented an air suspension coater that efficiently applied film coating compositions.[2–4] This stimulated renewed interest in tablet coating technology, and for the next 12 to 15 years, several hundred patents and research papers on the subject were published. The invention by Dr. Wurster showed the merits of high airflow in the coating process, and eventually, a series of perforated coating pans (Accela-Cota,* Hi-Coater,† Driacoater‡) were developed as replacements for the coating pans of the 30s and 40s (Figs. 12-1, 12-2, and 12-3).

In this chapter, the current state of tablet coating and the opportunities for continued improvement are presented.

Tablet Coating Principles

The application of coating to tablets, which is an additional step in the manufacturing process, increases the cost of the product; therefore, the decision to coat a tablet is usually based on one or more of the following objectives:

1. To mask the taste, odor, or color of the drug.
2. To provide physical and chemical protection for the drug.
3. To control the release of the drug from the tablet.
4. To protect the drug from the gastric environment of the stomach with an acid-resistant enteric coating.
5. To incorporate another drug or formula adjuvant in the coating to avoid chemical incompatibilities or to provide sequential drug release.
6. To improve the pharmaceutical elegance by use of special colors and contrasting printing.

*Thomas Engineering, Hoffman Estates, IL.
†Vector Corporation, Marion, IA.
‡Driam Metallprodukt GmbH & Co. KG, Eriskirch, West Germany.

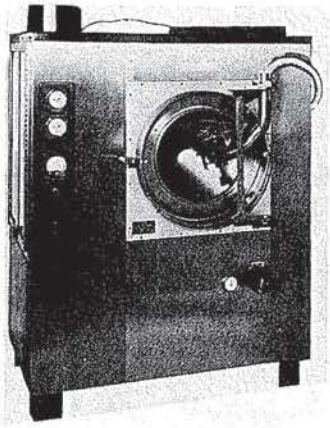

FIG. 12-1. *Accela-Cota system. (Courtesy of Thomas Engineering Inc., Hoffman Estates, IL.)*

The coating process can best be described by initially discussing the key factors that it comprises and then showing their complex interactions. There are three primary components involved in tablet coating:

1. Tablet properties.
2. Coating process.
   - Coating equipment.
   - Parameters of the coating process.
   - Facility and ancillary equipment.
   - Automation in coating processes.
3. Coating compositions. (Specific examples are discussed in the section entitled "Tablet Coating Processes.")

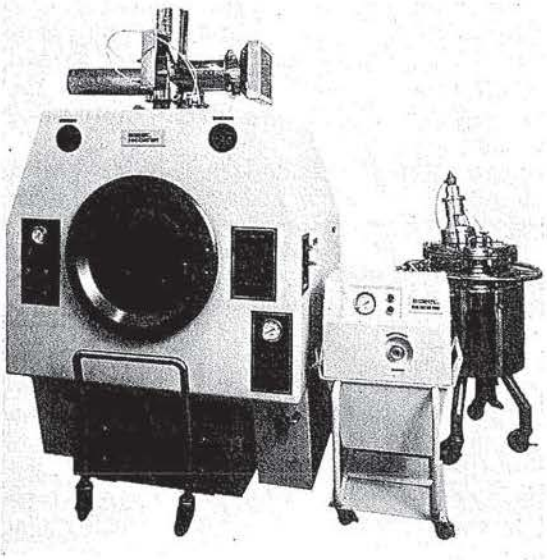

FIG. 12-2. *Hi-Coater system. (Courtesy of Vector Corporation, Marion, IA.)*

FIG. 12-3. *Driacoater system. (Courtesy of Driam Metallprodukt GmbH & Co. KG, Eriskirch, West Germany.)*

Tablet Properties. Tablets that are to be coated must possess the proper physical characteristics. In the coating process, the tablets roll in a coating pan or cascade in the air stream of an air suspension coater as the coating composition is applied. To tolerate the intense attrition of tablets striking other tablets or walls of the coating equipment, the tablets must be resistant to abrasion and chipping. Tablet surfaces that are brittle, that soften in the presence of heat, or that are affected by the coating composition tend to become rough in the early phase of the coating process and are unacceptable for film coating. Film coatings adhere to all exposed surfaces, so that any surface imperfection is coated and not eliminated. The quality of thin film coatings applied to compressed tablets usually depends much more on the quality of the starting tablet than on the time at which sugar coatings are applied. Sugar coatings, with their high solids content, dry more slowly and can fill many of the minor tablet surface imperfections that may occur in the early phase of the coating process.

In addition to a smooth surface, the physical shape of the tablet is important. When a coating composition is applied to a batch of tablets in a

coating pan, the tablet surfaces become covered with a tacky polymeric film. Before the tablet surface dries, the applied coating changes from a sticky liquid to a tacky semisolid, and eventually to a nontacky dry surface. The tablets must be in constant motion during the early drying phase or tablet agglomeration can occur. The ideal tablet shape for coating is a sphere, which allows tablets to roll freely in the coating pan, with minimal tablet-to-tablet contact. The worst shape is a square flat-faced tablet, in which case coating materials would collect between the surfaces to glue them together, like a stack of dominos or poker chips. For this reason, coated tablets have rounded surfaces; the more convex the surface is, the fewer difficulties will be encountered with tablet agglomeration.

A compressed tablet formulation includes many ingredients besides the active drug to provide a readily compressible, resilient, and rapidly dissolving dosage form. The resulting surface properties of the tablet depend on the chemical nature of the ingredients utilized in the formulation. For the coating to adhere to the tablet, the coating composition must wet the surface. Hydrophobic tablet surfaces are difficult to coat with aqueous-based coatings that do not wet the surface. The composition of the coating formulation can be adjusted, however, through the addition of appropriate surfactants to reduce the surface tension of the coating composition and improve coating adhesion.

Coating Process. The principles of tablet coating are relatively simple. Tablet coating is the application of a coating composition to a moving bed of tablets with the concurrent use of heated air to facilitate evaporation of the solvent. The distribution of the coating is accomplished by the movement of the tablets either perpendicular (coating pan) or vertical (air suspension coater) to the application of the coating composition.

Equipment. Most coating processes use one of three general types of equipment: (1) the standard coating pan, (2) the perforated coating pan, or (3) the fluidized bed (air suspension) coater. The general trend has been toward energy-efficient, automated systems to shorten the total coating time and reduce operator participation in the coating process. In addition, several pharmaceutical companies have developed their own coating equipment or made modifications in standard equipment to accommodate their particular coating processes. Most of the systems, however, are based on three basic designs.

Conventional Pan System. The standard coating pan system consists of a circular metal pan mounted somewhat angularly on a stand. The pan is 8 to 60 inches in diameter and is rotated on its horizontal axis by a motor (Fig. 12-4). Heated air is directed into the pan and onto the tablet bed surface, and is exhausted by means of ducts positioned through the front of the pan (Fig. 12-5). Coating solutions are applied to the tablets by ladling or spraying the material onto the rotating tablet bed. Use of atomizing systems to spray the liquid coating material onto the tablets produces a faster, more even distribution of the solution or suspension. Spraying can significantly reduce drying time between solution applications in sugar coating processes and allows for continuous application of the solution in film coating.

A significant improvement in the drying efficiency of the standard coating pan is achieved by the Pellegrini pan (Fig. 12-6), the immersion-sword (Fig. 12-7), and the immersion-tube systems (Fig. 12-8). The Pellegrini system has a baffled pan and a diffuser that distributes the drying air uniformly over the tablet bed surface. Newer models are completely enclosed, which further increases their drying efficiency and facilitates automated control. With the immersion-sword system, drying air is introduced through a perforated metal sword device that is immersed in the tablet bed. The drying air flows upward from the sword through the tablet bed. Since the air is more intimately mixed with the wetted tablets, a more efficient drying environment is provided. Coating solutions are applied by an atomized spray system directed to the surface of the rotating tablet bed. With the immersion-tube system, a tube is immersed in the tablet bed. The tube delivers the heated air, and a spray nozzle is built in the tip of the tube. During this operation, the coating solution is applied simultaneously with the heated air from the immersed tube. The drying air flows upward through the tablet bed and is exhausted by a conventional duct. Relatively rapid processing times have been reported for both film and sugar coating with this system.[5]

Both the immersion-sword and the immersion-tube systems have been introduced in Europe, and they are adaptable to conventional coating pans.

Perforated Pan Systems. In general, all equipment of this type consists of a perforated or partially perforated drum that is rotated on its horizontal axis in an enclosed housing. In the Accela-Cota and Hi-Coater systems, drying air is directed into the drum, is passed through the tablet bed, and is exhausted through perforations in the drum (Figs. 12-9 and 12-10). The Driacoater introduces drying air through hollow perforated ribs located on the inside periphery of

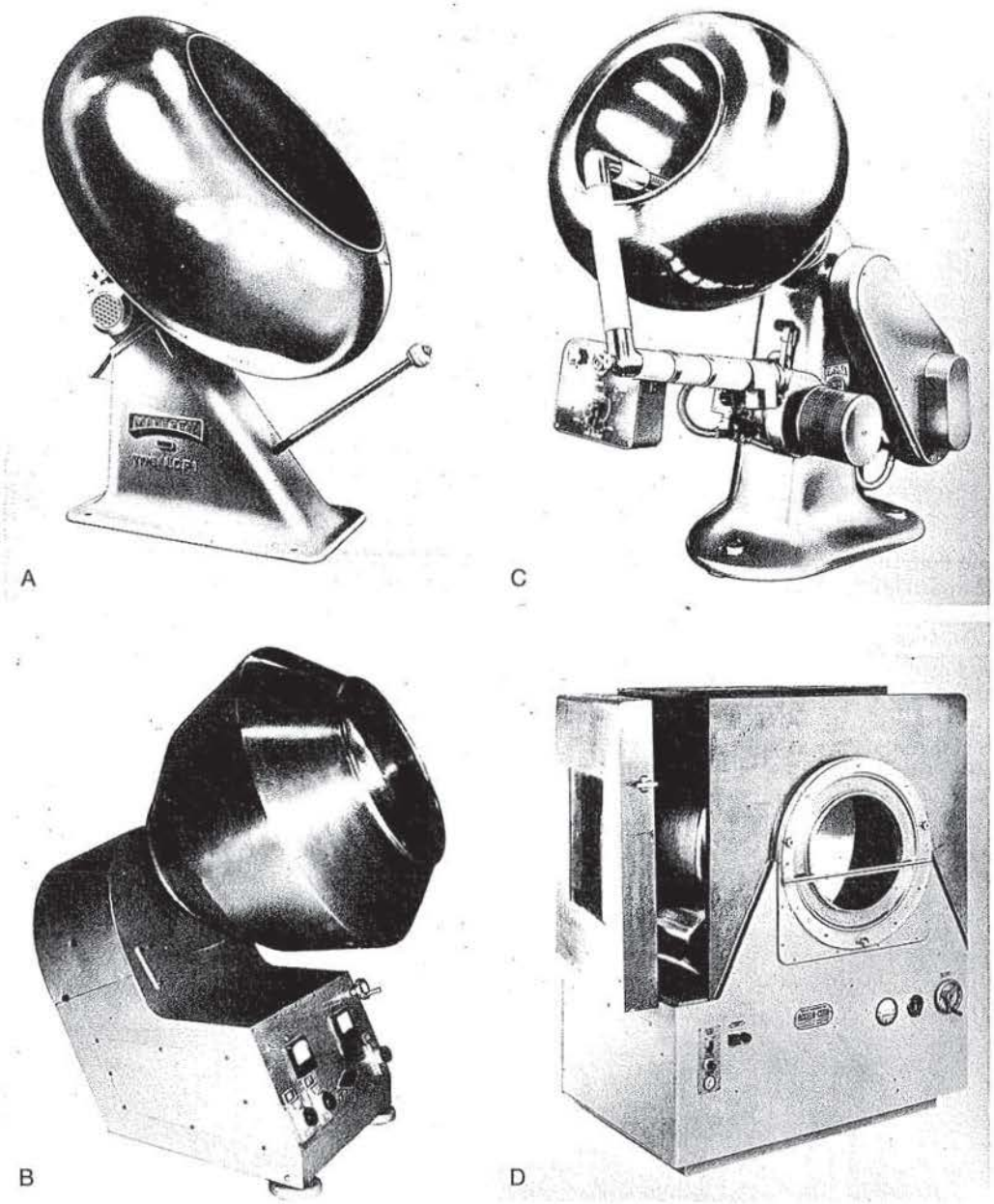

FIG. 12-4. *Standard coating pans.* A, B, *Pan shapes.* C, D, *Air sources. (Courtesy of Thomas Engineering Inc., Hoffman Estates, IL.)*

the drum (Fig. 12-11). As the coating pan rotates, the ribs dip into the tablet bed, and drying air passes up through and fluidizes the tablet bed. Exhaust is from the back of the pan.

The Glatt coater is the latest perforated pan coater to be introduced in the industry (Fig. 12-11A). In the Glatt coater, drying air can be directed from inside the drum through the tablet bed and out an exhaust duct; alternatively, with an optional split-chambered plenum, drying air can be directed in the reverse manner up through the drum perforations for partial fluidization of the tablet bed. Several airflow configurations are possible.

In all four of these perforated pan systems, the coating solution is applied to the surface of the

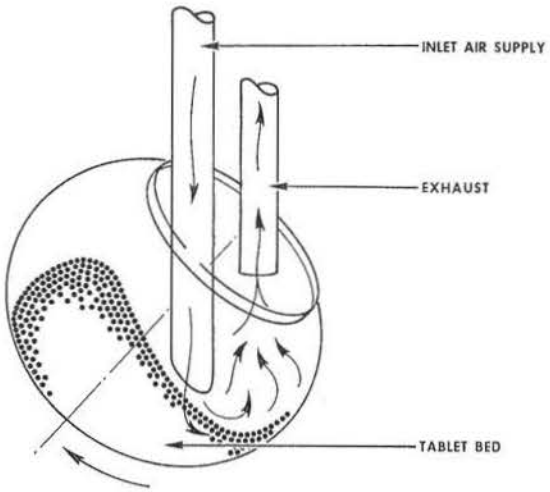

FIG. 12-5. *Diagram of standard coating pans.*

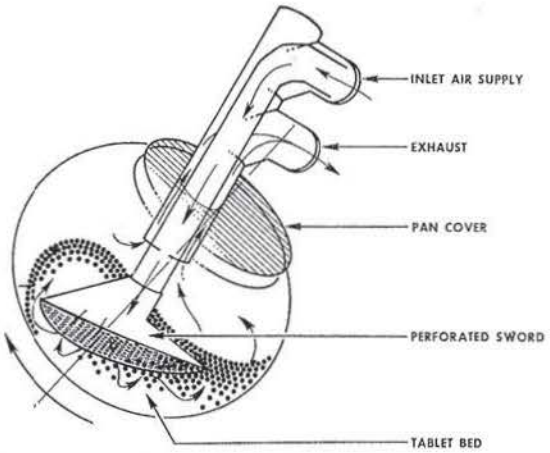

FIG. 12-7. *Simplified diagram of Glatt immersion-sword system.*

rotating bed of tablets through spraying nozzles that are positioned inside the drum.

Perforated pan coaters are efficient drying systems with high coating capacity, and can be completely automated for both sugar coating and film coating processes.

Fluidized Bed (Air Suspension) Systems. Fluidized bed coaters are also highly efficient drying systems. Fluidization of the tablet mass is achieved in a columnar chamber by the upward flow of drying air (Figs. 12-12 and 12-13). The airflow is controlled so that more air enters the center of the column, causing the tablets to rise in the center. The movement of tablets is upward through the center of the chamber. They then fall toward the chamber wall and move downward to re-enter the air stream at the bottom of the chamber. In some units, a smaller column(s) is used to direct tablet movement within the main column. Coating solutions are continuously applied from a spray nozzle located at the bottom of the chamber or are sprayed onto the top of the cascading tablet bed by nozzles located in the upper region of the chamber.

Tablet cores that are friable and prone to chipping and edge abrasion may be difficult to coat even under optimum conditions in the fluidized

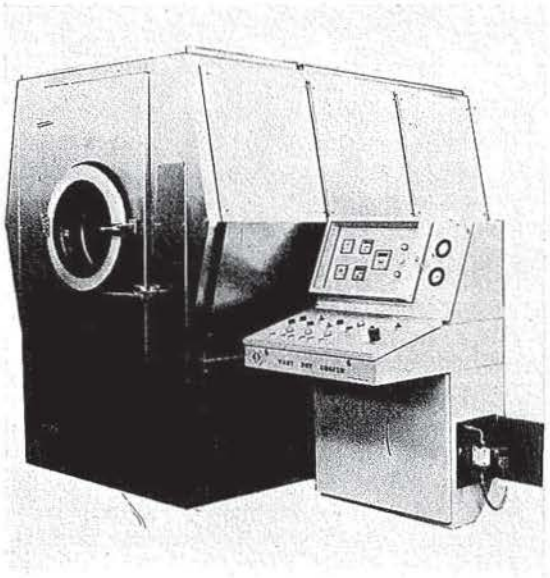

FIG. 12-6. *Pellegrini pan (enclosed) system. (Courtesy of Nicomac, Milan, Italy.)*

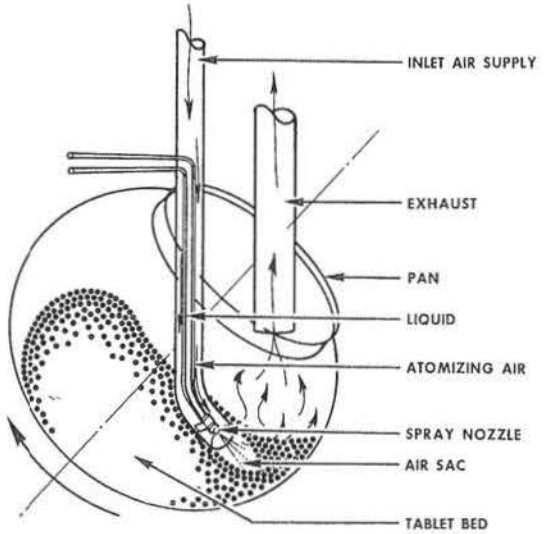

FIG. 12-8. *Diagram of immersion-tube system. (From Demmer et al.[5])*

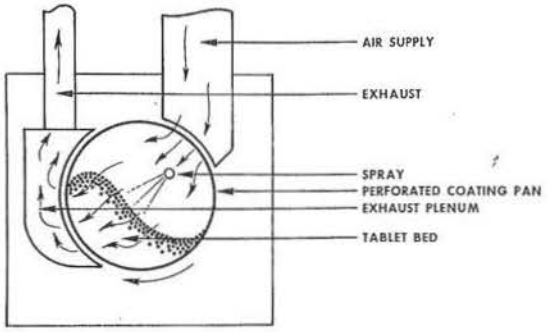

FIG. 12-9. *Simplified diagram of Accela-Cota system.*

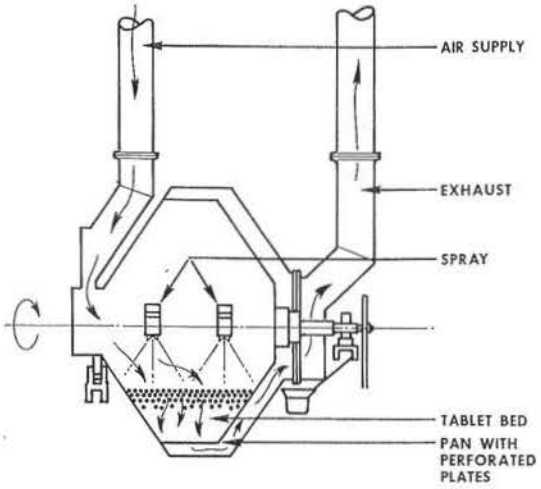

FIG. 12-10. *Simplified diagram of Hi-Coater system.*

bed systems, owing to the relatively rough tablet-to-tablet impact and tablet-chamber contact.

*Spray Application Systems.** The two basic types of systems used to apply a finely divided (atomized) spray of coating solutions or suspensions onto tablets are (1) high-pressure, airless and (2) low-pressure, air-atomized. The principal difference in the two types is the manner in which atomization of the liquid is achieved.

In the airless spray system, liquid is pumped at high pressure (250 to 3000 pounds per square inch gauge (psig)) through a small orifice (.009 inch to .020 inch id) in the fluid nozzle (Fig. 12-14), which results in a finely divided spray. The degree of atomization and the spray rate are controlled by the fluid pressure, orifice size, and viscosity of the liquid. Because of the small orifice, suspended solids in the coating composition must be finely milled or filtered to prevent orifice blockage.

In the low-pressure air-atomized system, liquid is pumped through a somewhat larger orifice (0.020 inch to 0.060 inch id) at relatively low

*Suppliers of spray application systems include (1) Spraying Systems Co., Wheaton, IL; (2) Graco Inc., Minneapolis, MN; (3) Vector Corp., Marion, IA; (4) Binks Manufacturing Co., Franklin Park, IL; (5) Nordson Corp., Amherst, OH.

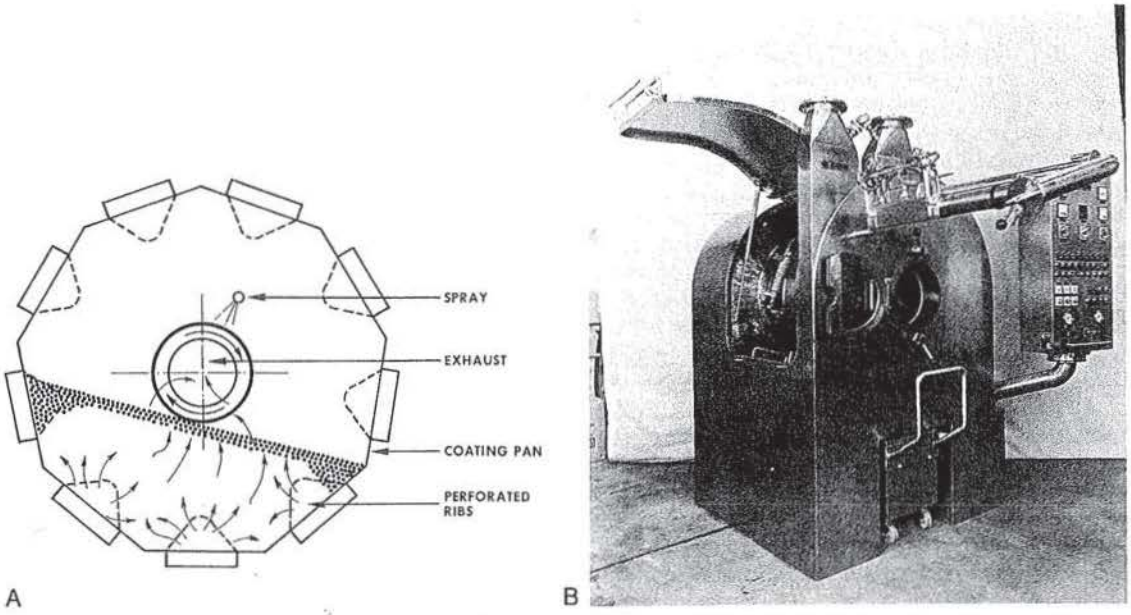

FIG. 12-11. A, *Diagram of Driacoater pan.* B, *Glatt coater. (Courtesy of Glatt Air Techniques Inc., Ramsey, NJ.)*

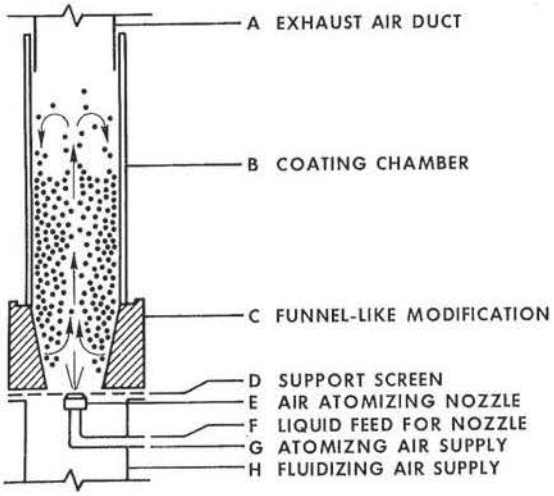

FIG. 12-12. *Diagram of a fluidized bed coater.*

pressures (5 to 50 psig) (Fig. 12-15). Low-pressure (10 to 100 psig) air contacts the liquid stream at the tip of the atomizer, and a finely divided spray is produced. The degree of atomization is controlled by the fluid pressure, fluid cap orifice, viscosity of the liquid, air pressure, and air cap design.

Both airless and air atomizing systems can be used effectively. Originally, airless systems were primarily used in air suspension coaters, but now the choice depends on the coating solution formula and on the process developed for a particular product.

Parameters. The following discussion of the coating process focuses primarily on perforated coating pans, as they are the most widely used equipment in the industry. However, the principles of the coating pan method are equally applicable to air suspension coating, with the exception that a portion of the air in the air suspension coater is used to suspend or move the tablets.

During the coating process, the tablets move through an application zone in which a portion of the tablets receive some coating. Outside this zone, a portion of the applied coating composition may be physically transferred from the coated tablets to adjacent ones, or even to the surface of the coating equipment. Most of the time, the tablets are in a drying mode moving away from the application zone and are recycled repeatedly through the application zone. The coating application and heated airflow can be continuous or intermediate, depending on the coating composition and drying conditions. In a continuous coating operation, the coating opera-

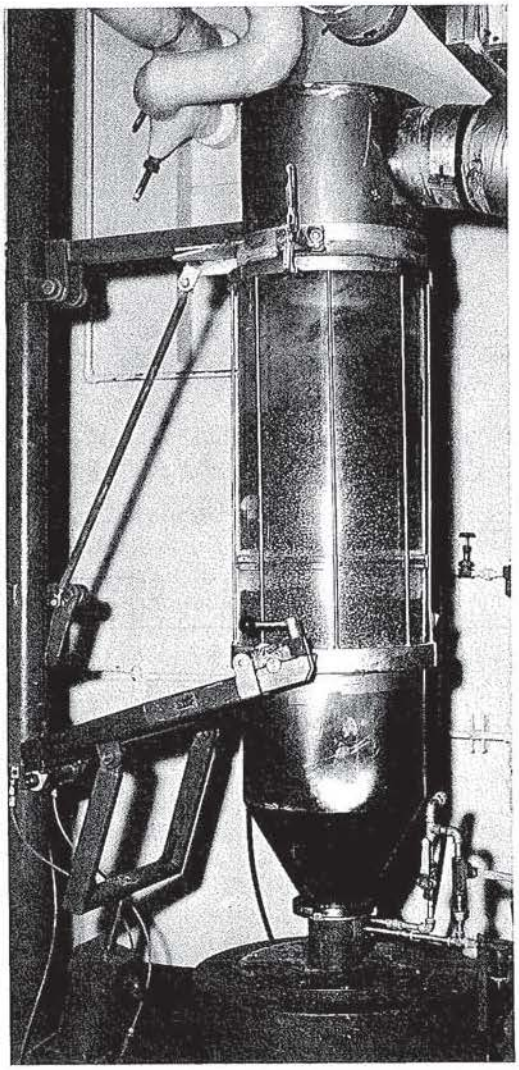

FIG. 12-13. *Fluidized bed coater. (Courtesy of Abbott Laboratories, North Chicago, IL.)*

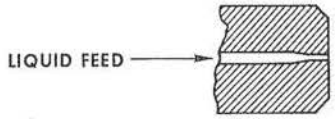

FIG. 12-14. *Simplified diagram of a high-pressure, airless nozzle.*

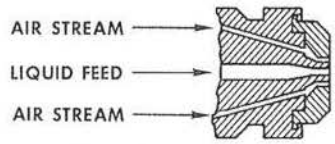

FIG. 12-15. *Simplified diagram of a low-pressure, air-atomized nozzle.*

tion is maintained essentially at equilibrium, where the rate of application of the coating composition equals the rate of evaporation of the volatile solvents. Deviation from this equilibrium results in serious coating problems. Mathematical modeling of the aqueous coating process has been accomplished by Stetsko and associates,[6] and by Reiland and associates.[7] These basic studies have formed the basis for the automated coating systems described later in the chapter.

A better appreciation of the balancing act that must be maintained in the coating process can be visually shown as follows:

$$\textit{Inlet}\ A(T_1, H_1) + C_1(S) + pSA_1 \xrightarrow{E} A\ (T_2, H_2) + C_2 + pSA_2\ \textit{Exhaust}$$

where A(T, H) is the air capacity, C(S) is the coating composition, pSA is the tablet surface area, and E is the equipment efficiency.

Air Capacity, A(T, H). This value represents the quantity of water or solvent that can be removed during the coating process, which depends on the quantity of air flowing through the tablet bed (CFM), the temperature of the air (T), and the quantity of water that the inlet air contains (H). This relationship can best be illustrated by using a psychrometric chart from an engineering handbook. The chart graphically shows the relationship between air temperatures and the quantity of water that air can contain at various relative humidities (RH).

For example, if the temperature of the inlet air is 100°F at about 10% RH it contains 30 g H_2O per pound of dry air. During the coating operation, water is evaporated from the applied aqueous coating solution, and the air temperature falls. The temperature of the exit air depends on the amount of water it contains. If the exit temperature is 75°F, the fall in temperature of 25°F is primarily due to evaporation of water, and the exit air contains 70 g of H_2O per pound of dry air (about 55% RH). Saturating the exit air yields a wet bulb temperature of 63.5°F.

Given the operating conditions, it is possible to know if the application rate is approaching the capacity of the drying system. Only a small portion of the tablet bed (pSA) receives coating at any given time; the exit temperature therefore measures the average of temperature conditions associated with tablets that are completely dry to those of tablets partially coated with the coating composition.

Coating Composition, C(S). The coating contains the ingredients that are to be applied on the tablet surface and the solvents, which act as carriers for the ingredients. These solvents are essentially removed during the coating process. The inlet air provides the heat to evaporate the water. The exhaust air becomes cooler and contains more water, owing to the evaporation of the solvent from the coating composition (see preceding example). If water is applied to a nonpenetrating surface, the relationship between inlet air (temperature/humidity) and exhaust air at a given spray rate can be clearly demonstrated. Tablet surfaces are permeable to the applied coating solution, which can cause coating difficulties. Most of the coating composition is solvent, so that rapid removal is necessary to prevent adverse effects on tablet integrity; however, high temperatures needed to achieve rapid drying may be detrimental to the stability of the drug in the tablet and may prevent partial distribution of the coating that occurs with movement of the tablets outside the application zone. The drying characteristic of the film must also be considered in determining the rate of application. In general, more viscous, aqueous-based coating compositions use movement of the tablets outside the application zone to produce partial distribution of the coating; longer drying periods are required so that intermittent coating application may be used. Thin, rapidly drying formulations dry quickly on the tablet surface, allowing constant application by efficient atomization of the coating solution.

Tablet Surface Area, pSA. The quality of the tablets needed for coating has already been considered, but the size of the tablet and the presence of debossed features also affect the coating conditions. The total surface area per unit weight decreases significantly from smaller to larger tablets. Application of a film with the same thickness requires correspondingly less coating composition. For example, when film coating a small pan load (20 kg) of tablets, a 0.281-inch round convex tablet that has a thickness of 0.114 inch requires 40% more coating than when the same coating thickness is applied to a 0.438-inch round convex tablet of 0.202-inch thickness.

In the coating process, only a portion of the total surface area (pSA) is coated. The balance consists of partially coated tablets being dried or dried tablets to be further coated in the application zone. Continuous partial coating and recycling eventually results in fully coated tablets.

The addition of small product identity markings or intagliations further complicates the coating process. The size of the atomized coating droplet must be smaller and better controlled as the features to be coated become smaller.

Equipment Efficiency, E. Tablet coaters use the expression "coating efficiency," a value ob-

tained by dividing the net increase in coated tablet weight by the total nonvolatile coating weight applied to the tablets. Ideally, 90 to 95% of the applied film coating should be on the tablet surface. Any quantity less than that suggests that improvements in the coating operation should be sought. Coating efficiency for conventional sugar coating is much less, and 60% would be acceptable. This significant difference in coating efficiency between film and sugar coating relates to the quantity of coating material that collects on the pan walls. With an efficient film coating process, little coating material accumulates on the wall, but with sugar coating, the pan walls become thickly covered with coating. A common cause of low film coating efficiency is that the application rate is too slow for the coating conditions (large tablet surface area, high airflow, and high temperature). This results in drying part of the coating composition before it reaches the tablet surfaces, so that it is exhausted as dust.

Facility and Ancillary Equipment. The facility required for any coating operation should be designed to meet the requirements of current Good Manufacturing Practices (GMPs) as set forth in the latest revision of the Code of Federal Regulations, Title 21, Part 211. Adequate space is needed not only for the coating equipment, but also for solution preparation and in-process storage. The specific safety requirement for coating areas depends on the nature of the solvent. Where explosive or toxic concentrations of organic solvent could occur, during either solution preparation or the coating operation, electrical explosion-proofing and specialized ventilation are required.

Treatment of the exhaust air from the coating operation may be desired to recover expensive organic solvents or to prevent solvents and particulate from entering the atmosphere. Local, state, and federal Environmental Protection Agency (EPA) regulations define the limits of organic solvent and particulate allowed in the atmosphere.

Compliance with the regulations can be extremely expensive, and this cost factor should be considered in developing a new coating. A major advantage of totally aqueous-based film coating is that all direct and indirect expenses relating to the purchase, handling, and environmentally acceptable removal of the organic solvent are circumvented.

Other equipment is needed to support the coating operation. Solution preparation requires tanks, filters, and mixers. A colloid mill or ball mill may be needed for the homogeneous dispersion of insoluble solids in the liquid coating mixture. Jacketed tanks may be needed for keeping some solutions at an elevated temperature.

The coating liquid can be supplied to the nozzle system of the coating equipment by means of portable pressure tanks or various pumping systems.

Automation. There is little published information providing details of automated coating processes. A review article by Thomas discusses details of a programmable controller for pan coating systems.[8] Within the last 6 to 8 years, automation has been achieved in sugar coating and film coating (nonaqueous and aqueous) systems. Through a series of sensors and regulating devices for temperature, airflow, spray rate and pan speed, a feedback control of the process is maintained. Precise automated control of such a dynamic process is possible only with the help of the programmable controller. As in all automated processes, a manual bypass should be built into the system to accommodate any special applications or equipment malfunctions. For process automation, the perforated pans are preferred over the old conventional coating pans because of their better efficiency. Figure 12-16 represents a completely automated system used for film or sugar coating. As new tablet manufacturing plants are built by major pharmaceutical companies, varying degrees of automation are built into the tablet coating process. These automated coating systems are either designed by coating equipment manufacturers or developed by individual companies and tailored to their specific equipment and/or products. A detailed description of such a system is provided by V. Sharma et al.[9].

Tablet Coating Processes

In most cases, the coating process is the last critical step in the tablet production cycle. The successful application of the coating solution formula to a tablet provides the visual characteristics for the product; thus, the quality of the product may be judged on this final production step. The type of process chosen depends on the type of coating that is to be applied, the durability (toughness) of the tablet core, and the economics of the process. Because of the ever-increasing cost of energy and labor, the cost of organic solvents, and the associated environmental constraints, the economics of the process is receiving greater emphasis. Sugar coating is still a widely used coating process because of the excellent tablet appearance it achieves.

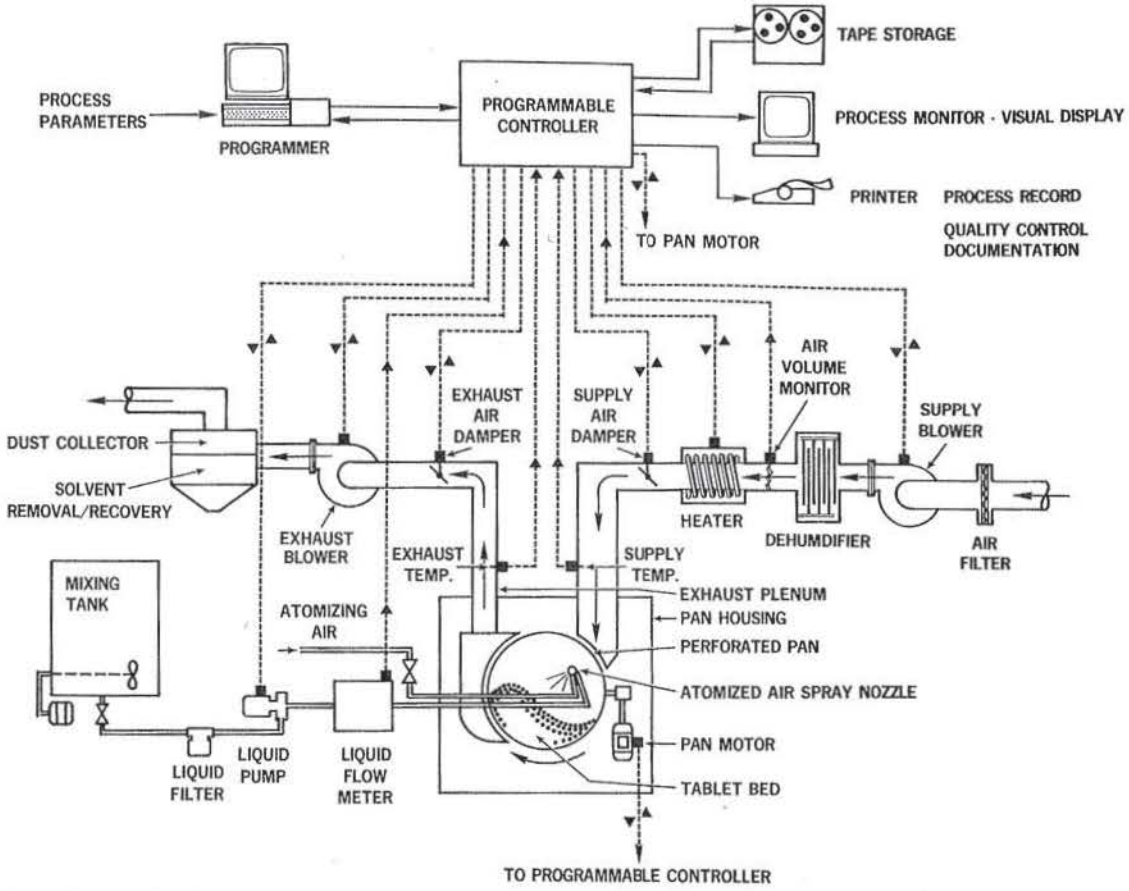

FIG. 12-16. *Diagram of an automated coating system.*

Sugar Coating

The sugar coating process involves several steps, the duration of which ranges from a few hours to a few days. A successful product greatly depends on the skill of the coating operator. This is especially true in the pan-ladling method, in which the coating solutions are poured over the tablet cores. The operator determines the quantity of solution to add, the method and rate of pouring, when to apply drying air, and how long or how fast the tablets should be tumbled in the pan. Newer techniques utilize spraying systems and varying degrees of automation to improve coating efficiency and product uniformity. Regardless of the methods used, a successful sugar coating process yields elegant, highly glossed tablets.

The basic sugar coating process involves the following steps: (1) sealing, (2) subcoating, (3) syruping (smoothing), (4) finishing, and (5) polishing.

The tablet cores preferably have deep convex surfaces with thin rounded edges to facilitate sugar coating. Since sugar coating tends to be long and vigorous, the cores should be relatively resistant to breakage, chipping, and abrasion.

Seal Coating

To prevent moisture penetration into the tablet core, a seal coat is applied. This is especially needed in pan-ladling processes, in which localized overwetting of a portion of the tablet bed occurs. Without a seal coat, the overwetted tablets would absorb excess moisture, leading to tablet softening or disintegration and affecting the physical and chemical stability of the finished product. In spray processes, it is possible to adjust the application of the subcoats and further coats so that localized overwetting does not occur. This adjustment thus eliminates the seal coating step. Shellac is an effective sealant, but tablet disintegration and dissolution times tend

to lengthen on aging because of the polymerization of the shellac. Zein is an alcohol-soluble protein derivative from corn that has also been used as an effective sealant. Lengthening dissolution times have not been reported on aging of zein seal coated tablets.

Subcoating

The subcoating is applied to round the edges and build up the tablet size. Sugar coating can increase the tablet weight by 50 to 100%. The subcoating step consists of alternately applying a sticky binder solution to the tablets followed by a dusting of subcoating powders and then drying. Subsequent subcoats are applied in the same manner until the tablet edges have been covered and the desired thickness is achieved. For spray processes, a subcoating suspension containing both the binder and the insoluble powder is sprayed intermittently on the tablet bed. With both methods of application, control of the drying rate is critical to obtaining a rapid application of the subcoat.

Syrup (Smoothing/Color) Coating

The purpose of this step is to cover and fill in the imperfections in the tablet surface caused by the subcoating step, and to impart the desired color to the tablet. This step perhaps requires the most skill. The first syrup coats usually contain some suspended powders and are called "grossing syrups." Dilute colorants can be added to this phase to provide a tinted base that facilitates uniform coloring in later steps. In general, no color is added until the tablets are quite smooth; premature application to rough tablets can produce a mottled appearance in the final coated tablets. In subsequent syruping steps, syrup solutions containing the dye are applied until the final size and color are achieved. In the final syruping or finishing step, a few clear coats of syrup may be applied.

Polishing

The desired luster is obtained in this final step of the sugar coating process. The tablets can be polished in clean standard coating pans, or canvas-lined polishing pans (Fig. 12-17), by carefully applying powdered wax (beeswax or carnauba) or warm solutions of these waxes in naphtha or other suitable volatile solvents.

*Example**

The basic sugar coating process is illustrated in this example. An infinite number of variations in the materials and processes are possible; however, the complexity of the process can be appreciated by the following example.

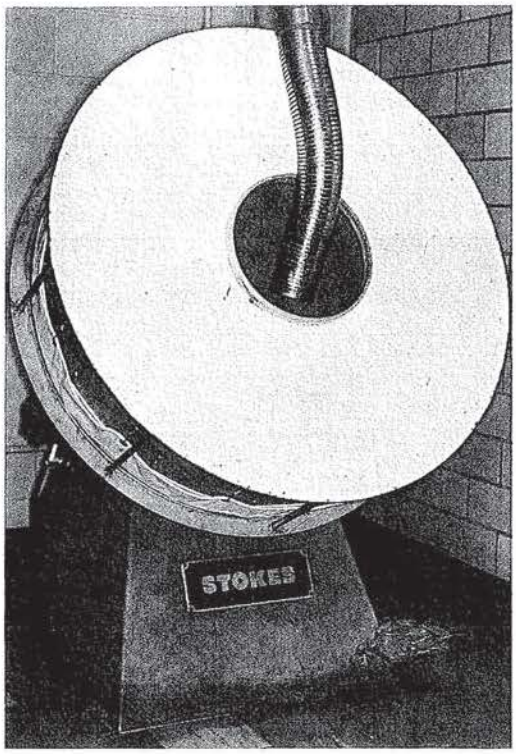

FIG. 12-17. *Canvas-lined polishing pan. (Courtesy of Warner-Lambert Co., Morris Plains, NJ.)*

I. Materials and Equipment
   Coating pans—Stainless steel, 40 inches in diameter, with variable speed control; or 48-inch Accela-Cota, with 2 to 3 air atomizing nozzles. Nozzles should have a fluid orifice of .040 to .060 inch. Set atomizing air to 30 to 40 psig.
   Tablet cores—55 to 70 kg of 3/8-inch standard convex tablets.
   NOTE: If desired, coating solutions may be poured or ladled onto the tablets. If this method is chosen, apply the solutions in a steady flow, with even distribution over the rotating tablet bed.

II. Process
   A. *Seal Coat*
      1. The specific advantage of using a spray system described in this example is that a faster and more even distribution of the coating materials is obtained. Start the tablets rolling (pan speed: 10 rpm). Set supply air to 30°C.

*See Table 12-1 for formulations used in this process.

TABLE 12-1. *Formulations Used in Sugar Coating*

Seal Coating Solutions	*Formula Variation*	
	I	*II*
Cellulose acetate phthalate		175 g
Zein	480 g	
Oleic acid, USP	60 g	
Propylene glycol, USP		52.5 g
Polyethylene glycol 4000	144 g	
Methylene chloride	480 ml	840 ml
Alcohol SD 3A 200-proof	q.s. to 2.4 L	q.s. to 1.75 L

Subcoating Solutions	*Formula Variation*			
	I	*II*	*III*	*IV*
Gelatin	60 g	5.4 kg		60 g
Acacia	60 g	2.7 kg	450 g	60 g
Sugar, cane	1500 g	53.7 kg		
Syrup, corn			450 g	1500 g
Syrup, USP			3.785 L	
Water, distilled	1.0 L	44.3 kg		1.0 L

Subcoating Powders	*Formula Variation*						
	I	*II*	*III*	*IV*	*V*	*VI*	*VII*
Kaolin		225 kg					
Dextrin		112 kg	185 kg				
Cocoa powder		60 kg					
Calcium carbonate, pptd			480 kg		7.72 kg		
Sugar, cane, powdered	4.1 kg	112 kg	240 kg	40 kg	0.9 kg	180 g	8.62 kg
Acacia, powdered	0.12 kg			6 kg		1 g	0.86 kg
Starch, corn	1.35 kg				0.9 kg	60 g	
Talc, USP	0.23 kg					1 g	
Calcium sulfate, NF							8.62 kg

Syrup Solutions	*Grossing Syrups*			*Heavy Syrups*		*Regular Syrups*	
	I	*II*	*III*	*I*	*II*	*I*	*II*
Colorant	q.s. ad	q.s. ad	q.s. ad	q.s. ad	q.s. ad	q.s. ad	q.s. ad
Subcoating powder	22.7 kg						
Calcium carbonate, light		7.75 kg	69 g				
Sugar, cane, powder	136 kg	22.7 kg	572 g	2.73 kg	181 kg	85 g	1.2 kg
Starch, corn		1.36 kg	69 g				
Syrup, USP		22.7 L		3.785 L	256 kg		
Water, distilled	76 kg		290 ml			q.s. 100 ml	1.0 L

Polishing Solutions	*Formula Variation*	
	I	*II*
Wax, carnauba, yellow	0.09 kg	10 g
Beeswax, white	0.09 kg	90 g
Wax, paraffin	0.02 kg	
Naphtha	3.785 L	1.0 L

Apply 3 applications of zein solution (see Table 12-1), 800 ml per application. Allow 15 to 20 min between applications to ensure that the tablets are dry. If tablets become tacky between applications, apply just enough talc to prevent sticking to the pan and to each other. Make sure that the solution is well distributed. Additional mixing by hand may be necessary to achieve this if pan design and baffling are inefficient.

B. *Subcoat*

Use any of the gelatin/acacia solutions and subcoating powders listed in Table 12-1.

1. Turn heat and inlet air off. Use exhaust only. Start pan speed at 10 rpm.
2. Apply 3 to 9 coats. Use 1.5 L of warm-gelatin/acacia solution for the first coat. Reduce subsequent amounts accordingly to obtain the correct thickness. Be sure that edges are covered. Thickness is checked volumetrically.
3. Allow at least 20 min between coats to permit adequate drying. Be sure the solution is rapidly and uniformly dispersed in the tablet bed. Dust with subcoating powder when tackiness develops. Apply subcoating powder until tablets roll freely and show no signs of tackiness.
4. After the last coat, jog the pan periodically for at least 2 to 4 hours to ensure dryness.

C. *Syrup (Smoothing/Color) Coat*

The syruping coat usually involves three basic phases: grossing syrup (a syrup solution with subcoating powders dispersed in it), heavy syrup, and regular syrup. Apply each step in the sequence outlined.

1. Remove excess dust in pan before starting. Turn on exhaust outlet air. Set inlet air temperature to provide an exhaust temperature of 45 to 48°C. Set pan speed at 12 rpm.
2. Apply 5 to 15 coats of the grossing syrup, just enough to wet the entire bed. Because this solution dries relatively quickly, uniform, rapid distribution must be provided. Apply successive amounts of grossing syrup immediately after each preceding application is drying and slightly dusty.
3. Apply several heavy-colored syrup coats in a similar manner until a specific tablet volume is attained.
4. Turn off heat, and reduce inlet and exhaust air.
5. Apply several coats of the regular-colored syrup solution to achieve a final smoothness, size, and color development.
6. Each coat of regular-colored syrup is applied as soon as the tablets exhibit a slightly frosted appearance. Do not allow them to become dusty.

D. *Finishing*

1. Make sure that the pan is clean.
2. Operate pan with the heat turned off, no supply, and greatly reduced exhaust air. Set pan speed at 12 rpm.
3. Apply 3 or 4 coats of regular-colored syrup rapidly, without permitting the tablet bed to frost or become dusty.
4. The last coats of regular syrup can be applied without colorant. This gives "depth" to the color and enhances the elegance of the coat.
5. Shut off exhaust air before applying the last coat. Apply coat; mix uniformly and shut off pan while the tablets are still damp. A quick jog every few minutes prevents sticking. After 15 to 30 min, stop jogging and leave tablets in pan to dry slowly overnight.

E. *Polishing*

Polishing can be done in the same pan as the sugar coating, but better results are obtained in canvas-lined pans.

1. Supply air, exhaust air, and heat should be turned off. Pan speed 12 rpm.
2. Apply 3 to 4 coats of warm polishing solution, approximately 300 ml per application.
3. Let solvent evaporate completely between coats.

Tablet coatings achieve their luster during the polishing phase. In the canvas-lined pans, the lining is used to transfer the waxes to the tablet surface and to provide a buffing action. The wax polishing solutions are usually poured onto the canvas, and the tablets pick up the wax shine as they tumble in the pan. The waxes can also be dusted onto the tablets. Care must be exercised to distribute the wax evenly to avoid wax spots on some tablets. Application of warm air can facilitate distribution.

The techniques used to obtain the desired product, especially in the pan-ladling process, are complex and can only be learned through practice. The beginner is advised to consult

the listed literature for specific techniques, materials, and precautions of the sugar coating processes.[10–15] The use of modern efficient automated systems is rapidly making manual techniques obsolete. Several automated processes have been described in the literature.[8,16–18]

Through the addition of cellulosic polymers, and other coating ingredients normally associated with film coating, much thinner sugar coatings have been attained.[19,20]

Film Coating

Since film coating originated from the pan sugar coating era, it is not surprising that the film coating process today still contains some of the process features associated with the early work. With the possible exception of the air suspension coater, film coating and sugar coating share the same equipment and process parameters.

Pan-Pour Methods

Pan-pour methods have been used for many years for film coating, but they have been supplanted by newer coating techniques that are faster and more reproducible. Coating compositions used in the earlier pan-pour methods were usually too viscous to be sprayed effectively. Tablets coated by pan-pour methods are subjected to alternate solution application, mixing and drying steps similar to pan-pour sugar coating. The method is relatively slow and relies heavily on the skill and technique of the operator to balance the steps to produce an acceptable product. Tablets that are film coated by pan-pour processes almost always require additional drying steps to remove latent solvents. Aqueous-based film coatings are not suitable for this method of application because localized overwetting inherent with the pan-pour process causes numerous problems ranging from surface erosion to product instability due to unacceptably high latent moisture content in the cores.

Pan-Spray Methods

The introduction of spraying equipment was the next evolution in improving the efficiency of film coating processes. Spraying lends versatility to the process and allows for automated control of liquid application. Spray patterns are selected to provide a continuous band across the tablet bed surface. Broad, flat spray patterns are usually chosen by selection of appropriate nozzle systems so that the entire width of the tablet bed can be covered by the spray from 1 to 5 nozzles.

Process Variables

Whether the coating process is in a conventional pan system or in one of the perforated pan systems previously described, certain elements of the process need to be controlled to ensure consistent product quality. The process is as important as the coating solution formulation; consequently development of a well-defined and well-controlled process should be a major concern of the formulator.

The variables to be controlled in pan-spray film coating processes are:

1. *Pan Variables*
   pan design/baffling
   speed
   pan load
2. *Process Air*
   air quality
   temperature
   airflow rate/volume/balance
3. *Spray Variables*
   spray rate
   degree of atomization
   spray pattern
   nozzle-to-bed distance

Since each listed variable is important to the overall success of the coating, further discussion is warranted.

Pan Variables. Pan shape, baffling, rotational speed, and loading all affect the mixing of the tablet mass. Uniform mixing is essential to depositing the same quantity of film on each tablet. The tablet coating adds an approximate increase in weight of only 2 to 5% to the tablet. Unacceptable color uniformity or enteric film integrity is encountered if the tablets are inadequately coated because of poor tablet movement in the coating pan.

Tablet shape can also affect mixing. Some tablet shapes may mix freely while other shapes may require a specific baffling arrangement to ensure adequate mixing. Baffles, however, provide a source for chipping and breakage if they are not carefully selected and used.

Pan speed affects not only mixing, but also the velocity at which the tablets pass under the spray. Speeds that are too slow may cause localized overwetting, resulting in the tablets sticking to each other or to the pan. Speeds that are too high may not allow enough time for drying

before the same tablets are reintroduced to the spray; again, this results in a rough coating appearance on the tablets. Pan speeds of 10 to 15 rpm are commonly used in the large pan coaters for nonaqueous film coating. Slower pan speeds (3 to 10 rpm) are used for aqueous film coating primarily to accommodate slower application rate and drying of the coating liquid. Selection of pan operating conditions depends on the equipment availability, type of tablets being coated, and the characteristics of the coating solution.

Spray Variables. The spray variables to be controlled are the rate of liquid application, the spray pattern, and the degree of atomization. These three variables are interdependent. In the airless, high-pressure system, all three variables are directly affected by fluid pressure and nozzle design. In the air-atomized, low-pressure system, the rate of liquid flow is most directly affected by the liquid pressure and liquid orifice size. The degree of atomization and spray pattern are most directly affected by atomizing air pressure, air volume, and the shape and design of the air jets in relation to the fluid stream.

The proper rate at which the coating solution should be applied depends on the mixing and drying efficiency of the system, in addition to the coating formula and core characteristics. There is a range in which the coating rate must operate to achieve the desired product quality or processing time. Overwetting and underwetting must be avoided in all coating operations.

A band of spray should be spread evenly over the tablet mass. In larger pans, more nozzles must be added to cover the tablet bed width. A spray pattern that is too wide could result in the application of coating directly to the pan surface, producing lower coating efficiency and wasted material. If the spray pattern is too narrow, localized overwetting may result, and the tablet-to-tablet coating uniformity will be poor. Thus, tablets need to make many more passes through the spraying area to be adequately coated. During the coating operation, the spray width can be adjusted by moving the nozzles closer or farther away from the tablet bed. In the air-atomized, low-pressure systems, adjusting the air pressure and/or direction accomplishes the same effect. The distance that the nozzle is from the tablet bed affects not only the spray width, but also the quantity of coating applied to individual tablets per pass under the spray.

Atomization is the process whereby the liquid stream is finely subdivided into droplets. The degree of atomization—the size and size distribution of the droplets—obtained from the spray nozzle is not an easily controllable parameter. The relationships between the orifice size, nozzle configuration, fluid pressure, atomizing air pressure, air volume, and fluid viscosity vary with each coating formulation. Manufacturing literature may provide the droplet size range expected from a particular nozzle type based on water; however, this type of data is inadequate for optimizing the nozzle performance in relation to the variety of solutions and suspensions used to coat tablets.

The degree of atomization, at present, can only be controlled empirically. Adjustments of either the fluid pressure on the airless high-pressure systems or the atomizing air pressure and air volume on the low-pressure systems change the degree of atomization. Higher pressures yield greater atomization. Atomization that is too fine causes some droplets to dry before reaching the tablet bed. This "spray-drying" effect can be readily detected as roughness on the tablet surface, especially in intagliations or as excess dust in the pan. Insufficient atomization may result in droplets that are too large reaching the tablet surface and causing localized overwetting, which could lead to sticking, picking, or a rough "orange-peel" effect.

Process Air Variables. The temperature, volume, rate, quality, and balance are parameters of the process air that need to be controlled to obtain an optimum drying environment for a particular coating process. The sensitivity of the film former and product core to heat largely determines the upper temperature at which the coating process is successful. In general, higher tablet bed and coating chamber temperatures are more conducive to rapid solvent evaporation, and consequently to faster coating rate. The limits to the air volume and rate depend on the overall design of the air-handling system and coating equipment. The upper end of the system's range is used most often. The more efficient the equipment design, the less air volume is needed for drying.

Supply air should have some degree of dehumidification. Seasonal fluctuations in the moisture content of incoming air can alter coating and drying conditions and possibly have adverse affects on the quality of the coating.

The balance between supply and exhaust airflow should be such that all dust and solvent are contained within the coating system.

Fluidized Bed Process

The fluidized bed systems have been successfully used for rapid coating of tablets, granules, and capsules. The coating solution formulations used with these processes are similar to those

used for the pan processes. Since air is used to move the tablets in the coating process, there are some specific process controls unique to air suspension coaters.

The chamber design, together with the process air, controls the fluidization pattern. Tablet shape, size, density, and quantity of load affect the ability of the tablet mass to be fluidized.

Adequate fluidization and drying depend on the volume and rate of the process air. Control of the process air is achieved by adjusting a variable speed blower or by using dampers to keep the tablet mass in a constant "fluid" motion inside the chamber. Too high an airflow results in excess tablet attrition and breakage. If the airflow rate is too low, the mass does not move fast enough through the spray region, and overwetting may occur. Fluidization may also be affected by the increase in weight or by changes in the frictional characteristics of the tablets during coating application. Consequently, periodic adjustment of the rate and volume will be necessary to maintain optimum fluidization.

During the coating operation, both the inlet and exhaust air temperatures are monitored. Evaporation of the solvent causes the exhaust air temperature to be cooler than the inlet. Any change in the rate of application of the coating solution can be monitored by the difference between the inlet and exit air temperatures.

Examples

Representative examples of organic and aqueous-based film coating formulations for use in laboratory perforated coating pan are provided.

I. Materials and Equipment
   Standard 24-inch Accela-Cota with 2 baffles.
   Spray system—Air-atomized spray nozzle with a .040-inch fluid orifice and a flat spray air cap.
   Pumping system—Pressure tanks.
   Coating materials—Description to follow (see example 1).
   Pan load—12 kg of 1/2-inch standard convex tablets.
   Operating conditions—Set pan speed at 12 to 15 rpm. Adjust supply air temperature to give an exhaust air temperature of 30°C during spray application. Use 40 to 50°C for the aqueous coating systems. Atomizing air pressure should equal 30 to 50 psig.

II. Process
   1. Load tablets into pan. Attach and adjust the spray nozzle to spray on upper half of tablet bed.
   2. Turn on heat, drying air, exhaust, and atomizing air.
   3. Intermittently jog the pan while tablets are warming.
   4. When exhaust temperature reaches 30°C, start spraying.
   5. Apply 3.0 to 4.0 L of color solution at a rate of 70 to 100 ml/min. Adjust rate downward if tablets become tacky.
   6. Apply 1.5 to 2.5 L of clear solution at a rate of 70 to 100 ml/min. Adjust rate downward if tablets become tacky. Allow tablets to dry in pan with air and heat on for 5 to 10 min.

One of the simplest film compositions would have all of the ingredients solubilized in the solvents, as in example 1.

Example 1: Hydroxypropyl Methylcellulose Nonaqueous Formula

(This formula can be applied by spraying or pouring systems.)

Hydroxypropyl methylcellulose 2910, USP, 15 cps	4%
Propylene glycol, USP	1.2%
Ethyl alcohol 200-proof	45%
Methylene chloride	q.s. ad 100%

The polymer is gradually added to the ethyl alcohol while the solvent is continuously agitated. A portion of the methylene chloride is added to this suspension, to solubilize the polymer. The propylene glycol is then added, and the remainder of the methylene chloride is added to obtain the proper volume.

The addition of insoluble colorants, opaquants, or flavors requires a milling step to facilitate their adequate dispersal.

Example 2: Cellulose Acetate Phthalate/Carbowax Nonaqueous Formula

(This formula should be poured, or diluted with appropriate solvents for spraying.)

Nonenteric Formula

Cellulose acetate phthalate, NF	5.0%
Polyethylene glycol 8000, NF	15.0%
Sorbitan monooleate, NF	0.3%
Dye yellow, D&C Lake #5	0.05%
Titanium dioxide	0.5%
Vanillin	0.1%
Castor oil	0.25%
Ethyl alcohol 200-proof	12.0%
Acetone	q.s. ad 100.0%

The cellulose acetate phthalate is dissolved in

the ethyl alcohol, sorbitan monooleate, and part of the acetone. To ensure proper dispersion, the dye, titanium dioxide, and vanillin are milled in a ball or high-energy mill, or are dispersed in acetone using a colloid mill. After the particle size reduction or dispersion has occurred, the colorants are added to the solution containing the polymer. The polyethylene glycol 8000 is melted and added with the castor oil to the polymer dispersion. The composition is brought to proper volume with acetone. This preparation must be kept slightly warm and must be properly agitated to assure proper distribution of the polyethylene glycol 8000 and the colorants in suspension.

Examples 3, 4, 5, and 6: Cellulose Aqueous Formula

(Aqueous systems should be sprayed.)

	3	4	5	6
Hydroxypropyl methyl-cellulose 2910, 15 cps	4.0%		2.0%	5.0%
Hydroxypropyl methyl-cellulose, 6 cps		6.0%	4.0%	
Hydroxypropyl cellulose				1.0%
Propylene glycol, USP	1.0%	1.0%		
Polyethylene glycol 400		0.5%	2.0%	1.0%
Water	q.s. 100.0%	100.0%	100.0%	100.0%

These polymers are soluble in water. Slowly add the polymer(s) to vigorously stirred water. Continue the agitation until the polymer(s) are solubilized, add propylene glycol or polyethylene glycol or both, then bring to proper volume with water. Colorants and pigments may be added after milling or dispersion in water.

Cellulose acetate phthalate was the primary synthetic enteric polymer used in the industry for many years. Now enteric acrylic resins and phthalate derivatives of polyvinyl acetate or hydroxypropyl methylcellulose are also available.

Example 7: Cellulose Acetate Phthalate Enteric Solution

(This system could be sprayed or poured.)

Cellulose acetate phthalate, NF	12.0%
Propylene glycol	3.0%
Sorbitan monooleate, NF	1.0%
Ethyl alcohol 200-proof	45.0%
Acetone	q.s. ad 100.0%

This solution is prepared in a manner similar to example 2. The cellulose acetate phthalate is dissolved in solvent mixture, and acetone is added to obtain the proper volume after polymer solvation is obtained.

The literature available from pharmaceutical polymer manufacturers provides numerous coating formulas utilizing their particular polymers. These formulas require the effective utilization of the favorable properties of the various polymers, plasticizers, and additives in the final coating composition to acquire a quality coated tablet.

Development of Film Coating Formulations

The decision to coat a tablet is usually the simplest one in the sequence that converts a compressed tablet to a coated tablet. The following questions must be answered concurrently with the decision to coat.

1. What is the purpose of the coating? Is it necessary to mask objectionable taste, color, or odor, or is it necessary to control drug release?
2. What tablet size, shape, or color constraints must be placed on the developmental work?

In the pharmaceutical industry, the color, shape, and size of the final coated tablet is important to marketing, and these properties have a significant influence on the decisions. Quality assurance is another function that exercises control over the product appearance. Quality assurance personnel evaluate the properties of the new product against the characteristics of existing products. In general, companies avoid marketing different products with the same appearance. There are a relatively limited number of colors available to the formulator, so that the product lines of many major pharmaceutical companies contain several coated tablets with various shades of red, yellow, green, and blue. Fortunately, tablet sizes and shapes can be easily varied; thus, the ability to select a tablet with a distinctive appearance is unlimited.

An experienced formulator usually takes the pragmatic approach and develops a coating formulation as a modification of one that has performed well in the past. The inexperienced coater or the formulator seeking a better coating system needs to start from a more basic position and essentially builds his coating composition from a primary film former. The effect of the addition of plasticizers, opaquants, colorants,

and the solvent system can then be individually and collectively assessed.

Film formulations can be preliminarily screened by spraying or casting films. Through the preparation of a series of films with slight changes in formula ingredients, it is possible to eliminate the obvious physical incompatibilities and poor film combinations rather quickly. One should recognize that this is only a screening study. Cast films and sprayed films can have different characteristics. In fact, some coating compositions yield poor cast films yet are effective tablet coatings.

Cast films can be prepared by spreading the coating composition on a Teflon, glass, or aluminum foil surface using a spreading bar to get a uniform film thickness. Many cast films adhere so well to glass that the film cannot be removed intact, but glass is certainly suitable for evaluating the appearance of the film. Many investigators who conducted water vapor permeability studies prepared their films by pouring their coating composition on mercury in petri dishes. This is convenient, as the surface area is constant, and the film can be readily removed from the liquid surface.

Sprayed films can be obtained by mounting a plastic-coated surface in a spray hood or coating pan. Care must be used in spraying the film to obtain a uniform film representative of the type achieved in tablet coating.

The physical appearance of these films can provide evidence of potential colorant or opaquant separation. Lack of color uniformity within the film could suggest that the insoluble additives have not been properly suspended or that some interaction has occurred between the ingredients. In addition, the films can be submitted for the following tests.

Water Vapor Permeability

If the coating is going to be used as a seal coat or to provide some physical protection for a tablet containing a water-unstable drug, then knowledge of the film's water vapor permeability should be assessed. (Detailed descriptions of the test procedure can be found in the literature.[21–24])

Film Tensile Strength

Strips of the film are tested on a tensile-strength tester by applying a known force at a constant rate. The elasticity and tensile strength/breaking stress of the films are evaluated. This test is particularly good when the effect of varying the concentration of a series of plasticizers or additives is being evaluated. Coating compositions that yield brittle films must be plasticized to obtain a more flexible film that is acceptable for tablet coating. Tensile-strength testing is one of the better ways to optimize the level of additives in the formulation.

Coated Tablet Evaluations

Once the preliminary screening of formulation variables has been accomplished, the candidate coating must now be studied under tablet coating conditions. Frequently, these studies are conducted on placebo tablets or on a group of placebo tablets with a limited number of drug tablets. The drug tablets must be of essentially the same shape, size, and density as the placebos, so that their patterns of movement in the coating pan are comparable. Obviously, there should be some distinctive tablet feature to permit separation of the tablets and allow evaluation of the two coated tablets. The technique of coating two different tablets at the same time has merit only if the surface properties of the two are equivalent. If two formulations, one having a hydrophilic surface and the other a hydrophobic surface, are aqueous-coated, the coating may preferentially adhere to one of the formulations.

Evaluation of the quality of coating on a tablet involves studying not only the film per se, but also the film-tablet surface interactions. A number of test methods can be employed.

1. Adhesion tests with tensile-strength testers have been used to measure the force required to peel the film from the tablet surface.[25–27] Rowe has been a prolific investigator in the area of film coating evaluation and the factors affecting film strength.[28,29]

2. Diametral crushing strength of coated tablets can be determined with a tablet hardness tester. Obviously, the resistance of the uncoated tablet to crushing will be a major factor in the test results. With this test, one is seeking information on the relative increase in crushing strength provided by the film and the contribution made by changes in the film composition.

3. The rate of coated tablet disintegration and/or dissolution must also be assessed. Unless the coating is intended to control drug release, the coating should have a minimal effect on tablet disintegration or dissolution.

4. Stability studies must be conducted on coated tablets to determine if temperature and humidity changes will cause film defects. Exposure of coated tablets to elevated humidity and measurement of tablet weight gain provide rela-

tive information on the protection provided by the film.

5. Some investigators have attempted to quantify film surface roughness, hardness, and color uniformity through instrumental means, but in general, visual inspection is sufficient to define relative coated tablet quality. A practical qualitative measure of the resistance of a coated tablet to abrasion can be obtained by merely rubbing the coated tablet on a white sheet of paper. Resilient films remain intact, and no color is transferred to the paper; very soft coatings are readily "erased" from the tablet surface to the paper.

Coating Formula Optimization

Optimization is usually associated with minor modifications in a basic formula. As discussed earlier, the basic or starting formula is obtained from past experience or from various sources in the literature. Modifications on this basic formula may be necessary to improve adhesion of the coating to the core; to decrease bridging of intagliations; to increase coating hardness; or to improve any property of the coating that the formulator deems deficient. Colorant and opaquant concentrations are usually fixed to achieve a predetermined shade. Changes of the polymer(s)-to-plasticizer ratio, however, or the addition of different plasticizers or polymers, are common modifications made in optimization of the coating.

This type of experimentation can be best achieved by conducting a fractional factorial type of study,* in which the concentration of a few plasticizers or polymers are evaluated in the same general coating formulation. Factorial studies allow evaluation of more variables with fewer experiments. The evaluation of each coating composition, however, must be conducted by a readily quantifiable criterion. For example, if the coating compositions are to be applied to tablets, can the coating conditions be effectively repeated? Can the properties of the film be measured by an objective testing system? The conditions used in the coating process frequently have as great an effect on the quality of the tablet coating as the coating composition. Studies on free films are much easier to conduct because there are test methods that can be used to evaluate changes in film properties with modifications in coating composition. Bonding of a film to a tablet surface or bridging of an intagliation can be measured, but the experimental error is much higher. Optimization of a particular property in free films should always be confirmed by the performance and appearance of the coated tablet.

The literature and patents cite numerous film coating compositions. The selection of a specific formulation depends on the coating equipment and conditions available, the intended purpose of the coating, and total solid load desired in the coating.

Materials Used in Film Coating

The coating materials may be a physical deposition of the material on the tablet substrate, or they may form a continuous film with a wide variety of properties depending upon the composition of the coating formulations. Examples of physical deposition of the coating materials are the techniques of sugar,[10,11] shellac,[30] and wax coatings.[31] During the last 40 years, a wide variety of polymers have been evaluated and are being used commercially for tablet coating. Further discussion of coating materials in this chapter is limited to synthetic polymers, solvents, plasticizers, colorants, opaquant-extenders, and miscellaneous coating solution components.

An ideal film coating material should have the following attributes:

1. Solubility in solvent of choice for coating preparation.
2. Solubility required for the intended use, e.g., free water-solubility, slow water-solubility, or pH-dependent solubility (enteric coating)
3. Capacity to produce an elegant looking product.
4. Stability in the presence of heat, light, moisture, air, and the substrate being coated. The film properties should not change with aging.
5. Essentially no color, taste or odor.
6. Compatibility with common coating solution additives.
7. Nontoxicity with no pharmacologic activity, and ease of application to the particles or tablets.
8. Resistance to cracking, and provision of adequate moisture, light, odor, or drug sublimation barrier when desired.
9. No bridging or filling of the debossed tablet surfaces by the film former.
10. Ease of printing procedure on high-speed equipment.

*Plackett-Burman statistical method.

No commercially available material fulfills all requirements of an ideal coating material. A pharmaceutical scientist usually formulates a coating solution to achieve certain desired properties for the film-coated product. The available film formers can be classified into nonenteric and enteric materials.

Film Formers

Nonenteric Materials

It is not possible to mention all polymers that have been investigated for filmcoating. The following discussion describes only some of the materials most commonly used by the pharmaceutical industry and is intended as a guide for the student or pharmaceutical scientist.

HYDROXYPROPYL METHYLCELLULOSE, USP

The polymer is prepared by reacting alkali-treated cellulose first with methyl chloride to introduce methoxy groups and then with propylene oxide to introduce propylene glycol ether groups. The resulting products are commercially available in different viscosity grades. This polymer is a material of choice for air suspension and pan-spray coating systems. The reasons for its widespread acceptance include (1) solubility characteristics of the polymer in gastrointestinal fluid, and in organic and aqueous solvent systems, (2) noninterference with tablet disintegration and drug availability, (3) flexibility, chip resistance, and absence of taste or odor, (4) stability in the presence of heat, light, air, or reasonable levels of moisture, (5) ability to incorporate color and other additives into the film without difficulty. The interaction of this polymer with colorants is rare.[32] Hydroxypropyl methylcellulose closely approaches the desired attributes of an ideal polymer for film coating. When used alone, the polymer has the tendency to bridge or fill the debossed tablet surfaces. A mixture of hydroxypropyl methylcellulose with other polymers or plasticizers is used to eliminate bridging or filling problems. This polymer is also used considerably in glossing solutions.[33]

METHYL HYDROXYETHYLCELLULOSE

This polymer is prepared by reacting alkali-treated cellulose first with methyl chloride and then with ethylene oxide. A wide variety of viscosity grades are available. Because of its structural similarity to hydroxypropyl methylcellulose, this polymer is expected to have similar properties. It is marketed in Europe, but because it is soluble in fewer organic solvents, it is not used as frequently as hydroxypropyl methylcellulose.

ETHYLCELLULOSE, NF

Ethylcellulose is manufactured by the reaction of ethyl chloride or ethyl sulfate with cellulose dissolved in sodium hydroxide. Depending on the degree of ethoxy substitution, different viscosity grades are obtained and available commercially. This material is completely insoluble in water and gastrointestinal fluids, and thus cannot be used alone for tablet coating. It is usually combined with water-soluble additives, e.g., hydroxypropyl methylcellulose, to prepare films with reduced water solubility properties. A combination of ethylcellulose with water-soluble additives has been widely used in preparing sustained-release coatings of fine particles and tablets. The polymer is soluble in a wide variety of organic solvents and is nontoxic, colorless, odorless, tasteless, and quite stable to most environmental conditions. Unplasticized ethylcellulose films are brittle and require film modifiers to obtain an acceptable film formulation. Banker and co-workers from Purdue University have developed aqueous polymeric dispersions utilizing ethylcellulose.[34] These pseudolatex systems are high-solids, low-viscosity compositions that have coating properties quite different from the regular ethylcellulose solutions. The material is commercially available through FMC Corporation as Aquacoat.*

HYDROXYPROPYLCELLULOSE, FCC

This material is manufactured by treatment of cellulose with sodium hydroxide, followed by a reaction with propylene oxide at an elevated temperature and pressure. It is soluble in water below 40°C (insoluble above 45°C), gastrointestinal fluids, and many polar organic solvents. This polymer is extremely tacky as it dries from a solution system and may be desirable for a subcoat, but not for a color or gloss coat. The polymer yields very flexible films. It is usually not used alone, but it is used in combination with other polymers to improve the film characteristics.

POVIDONE, USP

Povidone is a synthetic polymer consisting of linear 1-vinyl-2-pyrrolidinone groups. The degree of polymerization results in materials of

*FMC Corporation, 2000 Market Street, Philadelphia, PA 19103.

various molecular weight range. Povidone is usually available in four viscosity grades identified by their K values, which approximate K-15, K-30, K-60, and K-90. The average molecular weight of these grades are 10,000, 40,000, 160,000, and 360,000 respectively. The most common uses of povidone in pharmaceuticals (frequently K-30) are as a tablet binder and a tablet coating. It has excellent solubility in a wide variety of organic solvents, in water, and in gastric and intestinal fluids. When dry, povidone films are clear, glossy, and hard. The material is extremely tacky, but it is possible to modify the polymer properties by use of appropriate plasticizers, suspended powders, or other polymers. Although povidone is soluble in both acidic and basic fluids, it can be cross-linked with other materials to produce films with enteric properties. Povidone has been used to improve the dispersion of colorants in coating solutions to obtain a more uniformly colored film.

SODIUM CARBOXYMETHYLCELLULOSE, USP

This material is a sodium salt of carboxymethylcellulose and is manufactured by the reaction of soda cellulose with the sodium salt of monochloroacetic acid. It is available in low, medium, high, and extra high viscosity grades. Sodium carboxymethylcellulose is easily dispersed in water to form colloidal solutions, but it is insoluble in most organic solvents, and therefore is not a material of choice for coating solutions based on organic solvents. Films prepared with sodium carboxymethylcellulose are brittle, but adhere well to tablets. Partially dried films are tacky, however, so coating compositions must be modified with additives. Conversion to aqueous-based film coating with high coating efficiency equipment probably increases the usefulness of this polymer in coating systems.

POLYETHYLENE GLYCOLS

Polyethylene glycols (PEG) are manufactured by the reaction of ethylene glycol with ethylene oxide in the presence of sodium hydroxide at elevated temperature and under pressure. In addition to their other uses in formulations, they are used in film coating for which a wide variety of molecular weights are available. The materials with low molecular weights (200 to 600 series) are liquid at room temperature and are used as plasticizers for coating solution films. The materials with high molecular weights (series 900 to 8,000) are white, waxy solids at room temperature. These polymers are used in combination with other polymers to modify film properties. Combinations of polyethylene glycol waxes with cellulose acetate phthalate provide films that are soluble in gastric fluids. Such systems constituted one of the first commercially used nonenteric film coating processes.[35] Coats produced with the use of high-molecular-weight PEGs can be hard, smooth, tasteless, and nontoxic, but are somewhat sensitive to elevated temperatures.

ACRYLATE POLYMERS

A series of acrylate polymers is marketed under the trademark Eudragit.* Eudragit E is a cationic copolymer based on dimethylaminoethyl methacrylate and other neutral methacrylic acid esters, and is the only Eudragit material that is freely soluble in gastric fluid up to pH 5, and expandable and permeable above pH 5. This material is available as (1) organic solution (12.5%) in isopropanol/acetone, (2) solid material, or (3) 30% aqueous dispersion. Eudragit RL and RS are copolymers synthesized from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. These are available only as organic solutions and solid materials. These polymers produce films for the delayed-action (pH-independent) preparations similar to ethylcellulose formulations. These materials are widely used in Europe, but have limited use so far in the United States.

Enteric Materials

Enteric coating of pills and compressed tablets has existed for more than a century.[36] Some of the most important reasons for enteric coating are as follows:

1. To protect acid-labile drugs from the gastric fluid, e.g., enzymes and certain antibiotics.
2. To prevent gastric distress or nausea due to irritation from a drug, e.g., sodium salicylate.
3. To deliver drugs intended for local action in the intestines, e.g., intestinal antiseptics could be delivered to their site of action in a concentrated form and bypass systemic absorption in the stomach.
4. To deliver drugs that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form.
5. To provide a delayed-release component for repeat-action tablets.

*Rohm and Haas Co. Inc., Pharma. Gmbh., Germany.

An ideal enteric coating material should have the following properties:

1. Resistance to gastric fluids.
2. Ready susceptibility to or permeability to intestinal fluids.
3. Compatibility with most coating solution components and the drug substrates.
4. Stability alone and in coating solutions. The films should not change on aging.
5. Formation of a continuous (uninterrupted) film.
6. Nontoxicity.
7. Low cost.
8. Ease of application without specialized equipment.
9. Ability to be readily printed or to allow film to be applied to debossed tablets.

Pharmaceutical formulators have a wide choice of materials for use in developing an enteric coated granule, pellet, or tablet product. These materials range from water-resistant films to pH-sensitive materials. Some are digested or emulsified by intestinal juices, and some slowly swell and fall apart when solvated. Many formulators use a combination of the actions just listed to achieve the desired objective. Most commercially available enteric materials fail to display two or more of the ideal properties of an enteric coating material. The following section discusses some of the difficulties encountered in enteric formulations.

The United States Pharmacopeia (USP) disintegration test for enteric coated tablets requires that the tablets tolerate agitation in simulated gastric fluid test solution at 37 ± 2°C (no discs). After 1 hour of exposure in simulated gastric fluid, tablets should show no evidence of disintegration, cracking, or softening. Then a disc is added to each tube, and the test is continued using simulated intestinal fluid maintained at 37 ± 2°C as the immersion fluid, for a period of time equal to 2 hours or to the time limit specified in the individual monograph. If all the tablets disintegrate, the product passes the test. If 1 or 2 tablets fail to disintegrate completely, the test is repeated on 12 additional tablets. To pass the disintegration test, at least 16 out of 18 tablets should disintegrate.

All enteric coated tablets must meet these requirements. Passing the USP enteric test does not guarantee optimal bioavailability of a particular dosage form. Several situations complicate the absorption of drug from enteric coated tablets. The pH of the stomach contents may vary from 1.5 to 4.0, with about 10% of the patients having achlorhydria. The amount of gastric fluid may vary between individuals, and for the same individual from time to time. Gastric residence time for the dosage form may range from less than half an hour to more than 4 hours depending on the time of its administration, whether it was consumed with food, and if so, the type and quantity of food. The USP disintegration test does not require a qualitative or quantitative test for the active drug after agitation in artificial gastric fluid for 1 hour. Several commercially available enteric products passed the USP enteric test, but released varying amounts of drugs in simulated gastric fluid.[37] Most acid-labile drugs need protection between pH values 1 and 5. The pH of material approaching pylorus is expected to be about 5. An ideal enteric polymer should dissolve or become permeable near and above pH 5.

A common problem associated with the retardant type of polymers (non-pH dependent solubility), which act by mechanical hydrophobicity, is that to provide enteric effect, the film might be so thick that if the dosage form travels too fast through the gastrointestinal tract, solubilization in intestinal fluids may never be achieved. Commercial products have failed the enteric test both for lack of gastric protection and for lack of solubility in intestinal fluids.[38,39] Many others passed these in vitro tests, but failed to perform adequately when studied in vivo.[40]

A review of tablet coating by Porter summarizes the commercially available enteric polymers.[41]

CELLULOSE ACETATE PHTHALATE (CAP)

CAP has been widely used in the industry. It has the disadvantage of dissolving only above pH 6, and possibly delaying the absorption of drugs. It is also hygroscopic and relatively permeable to moisture and gastric fluids, in comparison with some other enteric polymers. CAP films are susceptible to hydrolytic removal of phthalic and acetic acids, resulting in a change of film properties. CAP films are brittle and usually formulated with hydrophobic-film forming materials or adjuvants to achieve a better enteric film. FMC Corporation has developed a patented aqueous enteric coating called Aquateric.[42] Aquateric coating is a reconstituted colloidal dispersion of latex particles (not a solvent solution coating system). It is composed of solid or semisolid polymer spheres of cellulose acetate

phthalate ranging in size from 0.05 to 3 microns with an average particle size of 0.2 micron. This material is currently being offered for potential industrial applications.

ACRYLATE POLYMERS

Two forms of commercially available enteric acrylic resins are Eudragit L and Eudragit S. Both resins produce films that are resistant to gastric fluid. Eudragit L and S are soluble in intestinal fluid at pH 6 and 7, respectively. Eudragit L is available as an organic solution (Isopropanol), solid, or aqueous dispersion. Eudragit S is available only as an organic solution (Isopropanol) and solid.

HYDROXYPROPYL METHYLCELLULOSE PHTHALATE*

Shin-Etsu Chemical Company has made three enteric polymers available commercially. These are derived from hydroxypropyl methylcellulose, N.F., by esterification with phthalic anhydride, and are marketed as HPMCP 50, 55, and 55S (also known as HP-50, HP-55, and HP-55-S). HPMCP is the trade name for hydroxypropyl methylcellulose phthalate. These polymers dissolve at a lower pH (at 5 to 5.5) than CAP or acrylic copolymers, and this solubility characteristic may result in higher bioavailability of some specific drugs.[43] For general enteric preparations, HP-55 is recommended by Shin-Etsu; HP-50 and HP-55S are recommended for special situations. These polymers are quite stable compared with CAP because of their absence of labile acetyl groups.

POLYVINYL ACETATE PHTHALATE (PVAP)†

PVAP is manufactured by the esterification of a partially hydrolyzed polyvinyl acetate with phthalic anhydride. This polymer is similar to HP-55 in stability and pH-dependent solubility. It is supplied as ready-to-use or ready-to-disperse enteric systems.

Solvents

The primary function of a solvent system is to dissolve or disperse the polymers and other additives and convey them to the substrate surface. All major manufacturers of polymers for tablet coating provide basic physical-chemical data on their polymers. These data are usually helpful to a formulator. Some important considerations for an ideal solvent system are as follows:

1. It should either dissolve or disperse the polymer system.
2. It should easily disperse other coating solution components into the solvent system.
3. Small concentrations of polymers (2 to 10%) should not result in an extremely viscous solution system (>300 cps), creating processing problems.
4. It should be colorless, tasteless, odorless, inexpensive, nontoxic, inert, and nonflammable.
5. It should have a rapid drying rate (the ability to coat a 300 kg load in 3 to 5 hours).
6. It should have no environmental impact.

The most widely used solvents, either alone or in combination are water, ethanol, methanol, isopropanol, chloroform, acetone, methylethylketone, and methylene chloride. Because of environmental and economic considerations, water is the solvent of choice; however, several polymers cannot be applied from aqueous systems. Drugs that readily hydrolyze in the presence of water can be more effectively coated with nonaqueous-solvent-based coatings. Such a process might require applying an initial sealing coat from an organic-based subcoating, followed by aqueous color and gloss coating. The use of organic-solvent-based film coatings will undoubtedly decrease as better aqueous systems are developed. It is unlikely, however, that organic solvents will be entirely supplanted.

Plasticizers

The quality of a film can be modified by the use of "internal" or "external" plasticizing techniques. Internal plasticizing pertains to the chemical modification of the basic polymer that alters the physical properties of the polymer. This aspect has been discussed earlier under different polymeric materials. By controlling the degree of substitution, the type of substitution, and the chain length, polymer properties can be altered significantly. Most often, the formulator uses external plasticizers as additives to the coating solution formula so that the desired effects are achieved for the film. An external plasticizer can be a nonvolatile liquid or another polymer, which when incorporated with the primary polymeric film former, changes the flexibility, tensile strength, or adhesion properties of the resulting film.

As the solvent is removed, most polymeric materials tend to pack together in three-dimen-

*Distributed by Biddle Sawyer Corporation, 2 Penn Plaza, New York, NY 10121.
†Supplied by Colorcon, Inc., West Point, PA 19486.

sional honeycomb arrangements.[44] The choice of plasticizer depends upon the ability of plasticizer material to solvate the polymer and alter the polymer-polymer interactions. When used in correct proportion to the polymer, these materials impart flexibility by relieving the molecular rigidity. The type of plasticizer(s) and its ratio to the polymer can be optimized to achieve the desired film properties. One should also consider the viscosity of the plasticizer; its influence on the final coating solution; its effect on film permeability, tackiness, flexibility, solubility, and taste; and its toxicity, compatibility with other coating solution components, and stability of the film and the final coated product.

A combination of plasticizers may be needed to achieve the desired effect. The concentration of the plasticizers depends on many factors, including the polymer chemistry, method of application, and the other components present in the system. Even changes in the drying rate or use of elevated temperatures may alter the influence of the plasticizer in the coating process. The presence of titanium dioxide, colorants, flavors, and other additives also affect the film former. Most film formers tolerate only a certain additive load, and beyond that limit, the film properties are adversely affected.

The amount and type of plasticizers to be used for any given polymer can be based on the polymer manufacturer's recommendations. Optimization of the plasticizer concentration must be based on the presence of the other additives. Concentration of a plasticizer is expressed in relation to the polymer being plasticized. Recommended levels of plasticizers range from 1 to 50% by weight of the film former. Some of the commonly used plasticizers are castor oil; propylene glycol; glycerin; low-molecular-weight polyethylene glycols of 200 and 400 series; and surfactants, e.g., polysorbates (Tweens), sorbitan esters (Spans), and organic acid esters. With the increasing interest in aqueous coating, water-soluble plasticizers, e.g., polyethylene glycols and propylene glycol, are used. Conversely, castor oil and Spans are used primarily for organic-solvent-based coating solutions. For an external plasticizer to be effective, it should be soluble in the solvent system used for dissolving the film former and plasticizer. The plasticizer and the film former must be at least partially soluble or miscible in each other.

Colorants

Coating solution formulations may contain a wide variety of components in addition to the film former, solvents, and plasticizers. Colorants may be soluble in the solvent system or suspended as insoluble powders. They are used to provide distinctive color and elegance to a dosage form. To achieve proper distribution of suspended colorants in the coating solutions requires the use of fine-powdered colorants (<10 microns). Repetitive production of colored coating solutions from different lots of the same colorant can be particularly difficult if colorant lots have different dye content, crystal form of dye, or particle size distribution. In general, the suspended colorants must be milled in the coating solvent or solution to attain a uniform dispersion of the colorants. Color variation in a product can be readily detected by the pharmacist and patient; therefore, the colors must be reproducible and stable.

The most common colorants in use are certified Food Drug and Cosmetic (FD&C) or Drug and Cosmetic (D&C) colorants. These are synthetic dyes or lakes of dyes. Lakes are derived from dyes by precipitating with carriers, e.g., alumina or talc. Lakes have become the colorants of choice for sugar or film-coating systems, as more reproducible tablet colors are attainable. Most commercially available lakes contain 10 to 30% of the pure dye content, but some lakes approach up to 50%. An occasional problem with the lake system might be the use of a solvent system that dissolves the dye, thereby establishing a time- and temperature-dependent equilibrium for leaching the dye from the lake system. Use of pure dye is recommended in such cases.

The concentration of colorants in the coating solutions depends on the color shade desired, the type of dye (i.e., dye versus the lake of the dye), and the concentration of the opaquant-extenders. If a very light shade is desired, a concentration of less than 0.01% may be adequate. On the other hand, if a dark color is desired, a concentration of more than 2.0% may be required. Since lakes contain less colorant, a larger concentration in solution is generally required.

The inorganic materials (e.g., iron oxides) and the natural coloring materials (e.g., anthocyanins, caramel, carotenoids, chlorophyll, indigo, flavones, turmeric, and carminic acid) are also used to prepare coating solutions.

A new line of colorants is being developed.[45] These colorants are nonabsorbable in the biologic system. This is accomplished by attaching dyes to polymers that are too large to be absorbed in the gastrointestinal tract and yet are resistant to degradation in the gastrointestinal tract. A magenta red dye is projected to be the first dye to be cleared for use.

A variety of products that are commercially available permit preparation of coating solution

Matrix Tablets

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blends of drug, retardant material, and additives to form a tablet in which drug is embedded in a matrix core of the retardant. Alternately, retardant-drug blends may be granulated prior to compression. Table 14-7 identifies examples of the three classes of retardant material used to formulate matrix tablets, each class demonstrating a different approach to the matrix concept. The first class consists of retardants that form insoluble or "skeleton" matrices; the second class represents water-insoluble materials that are potentially erodable; and the third class consists of polymers that form hydrophilic matrices. Loading doses are best included as the second layer of a two-layer tablet or in a coating applied to the matrix core.

Insoluble, inert polymers such as polyethylene, polyvinyl chloride, and acrylate copolymers have been used as the basis for many marketed formulations. Tablets prepared from these materials are designed to be egested intact and not break apart in the GI tract. Tablets may be directly compressed from mixtures of drug and ground polymer; however, if ethyl cellulose is used as the matrix former, a wet granulation procedure using ethanol can be employed. The rate-limiting step in controlling release from these formulations is liquid penetration into the matrix unless channeling (wetting) agents are included to promote permeation of the polymer matrix by water, which allows drug dissolution and diffusion from the channels created in the matrix. Formulations should be designed so that pore diffusion becomes rate-controlling, release is defined by equation (16) or (17), and the release profile is represented by curve C (Fig. 14-10). Drug bioavailability, which is critically dependent on the drug:polymer ratio, may be modified by inclusion of diluents such as lactose in place of polymer in low-milligram-potency formulations.[33]

Egested tablets contain unreleased drug in the core. In one study of polyvinyl chloride matrix tablets containing prednisolone disodium phosphate, egested tablets contained 72% of the maintenance dose for matrices containing 87% plastic and 2% drug, and 28% drug for matrices containing 84% plastic and 3% drug.[34] These forms of matrix tablets are not useful for high-milligram-potency formulations in which the polymer content would be insufficient to form a matrix, or for highly water-insoluble drugs in which dissolution in the matrix would become rate-limiting. Release of water-soluble drugs, however, should be unaffected by the amount of liquid, pH-value, enzyme content, and other physical properties of digestive fluids, unless the drug is in a salt form that precipitates within

TABLE 14-7. *Materials Used as Retardants in Matrix Tablet Formulations*

Matrix Characteristics	*Material*
Insoluble, inert	Polyethylene Polyvinyl chloride Methyl acrylate-methacrylate copolymer Ethylcellulose
Insoluble, erodable	Carnauba wax Stearyl alcohol Stearic acid Polyethylene glycol Castor wax Polyethylene glycol monostearate Triglycerides
Hydrophilic	Methylcellulose (400 cps, 4000 cps) Hydroxyethylcellulose Hydroxypropylmethylcellulose (60 HG, 90 HG, 25 cps, 4000 cps, 15,000 cps) Sodium carboxymethylcellulose Carboxypolymethylene Galactomannose Sodium alginate

the matrix pores on dissolution when penetrated by acid or basic media.

Waxes, lipids, and related materials form matrices that control release through both pore diffusion and erosion (curve D, Fig. 14-10). Release characteristics are therefore more sensitive to digestive fluid composition than to the totally insoluble polymer matrix. Total release of drug from wax-lipid matrices is not possible, since a certain fraction of the dose is coated with impermeable wax films. Release is more effectively controlled by the addition of surfactants or wicking agents in the form of hydrophilic polymers, which promote water penetration and subsequent matrix erosion.

Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized as a retardant base for many sustained release matrix formulations. Mixtures of (1:1) hydrogenated castor oil and propylene glycol monostearate and of carnauba wax and stearyl alcohol or stearic acid have been extensively studied as retardants for both water-soluble and water-insoluble compounds. Materials with melting points that are too low or materials that are too soft cannot be readily processed to form tablets with good physical stability. Such retardants as carnauba wax or hydrogenated castor oil provide the necessary physical characteristics to form an easily compressible stable matrix. If used singly, these materials excessively delay drug release.

Three methods may be used to disperse drug and additive in the retardant base. A solvent evaporation technique can be used, in which a solution or dispersion of drug and additive is incorporated into the molten wax phase. The solvent is removed by evaporation. Dry blends of ingredients may be slugged and granulated. A more uniform dispersion, however, can be prepared by the fusion technique, in which drug and additive are blended into the molten wax matrix at temperatures slightly above the melting point (approximately 90° C for carnauba wax). The molten material may be spray-congealed, solidified and milled, solidified and flaked, or poured on a cold rotating drum to form sheets, which are then milled and screened to form a granulation.

In the absence of additives, drug release is prolonged and nonlinear. Apparent zero-order release can be obtained by addition of additives such as polyvinyl pyrrolidone or polyoxyethylene lauryl ethers. In a study by Dahkuri et al., 10 to 20% hydrophilic polymer effectively controlled release from carnauba-wax/stearyl-alcohol matrices of tripelennamine hydrochloride.[35] Matrices prepared from carnauba-wax/polyethyleneglycol compositions have also been used to prepare sustained release theophylline tablets. The wax:glycol ratio could be adjusted to vary the release characteristics.

A novel approach to the development of a lipid matrix utilizes pancreatic lipase and calcium carbonate as additives, with triglycerides as retardants. The lipase is activated on contact with moisture and thus promotes erosion independent of intestinal fluid composition. The release profile is controlled by the calcium carbonate, since calcium ions function as a lipase accelerator.[36] In another technique, drug is mass-blended with stearyl alcohol at a temperature above its glass transition (approximately 60°C), and the mass is cooled and granulated with an alcoholic solution of zein. This formulation is claimed to produce tablets with stable release characteristics. Since natural waxes and lipids are complex mixtures, and a fusion process is usually required for processing, hardening with decrease in effective drug release on aging may be observed, owing to polymorphic and amorphous to crystalline transitions.

The third group of matrix formers represents nondigestible materials that form gels in situ. Drug release is controlled by penetration of water through a gel layer produced by hydration of the polymer and diffusion of drug through the swollen, hydrated matrix, in addition to erosion of the gelled layer (curve D, Fig. 14-10). The extent to which diffusion or erosion controls release depends on the polymer selected for the formulation as well as on the drug:polymer ratio. Low-molecular-weight methylcelluloses release drug largely by attrition, since a significant intact hydrated layer is not maintained. Anionic polymers such as carboxymethyl cellulose and carpolene can interact with cationic drugs and show increased dissolution in intestinal fluid. Carboxypolymethylene does not hydrate in gastric fluid. The best matrix former in this group is hydroxymethylcellulose 90 HG 15,000 cps, an inert polymer that does not adversely interact with either acidic or basic drugs, and that on contact with water slowly forms a gel that is more resistant to attrition. Release rates can be adjusted for low-milligram-potency formulations by replacing polymer with lactose. High drug:polymer ratios result in formulations from which drug release is controlled by attrition.[37]

The process used to prepare formulations for compression depends on the polymer and drug:polymer ratio. With high drug:polymer ratios, a wet granulation process is required. Low-milligram-potency formulations may be directly compressed or granulated using alcohol if the polymer is not in a form amenable to direct

and several members of the polyethylene glycol polymer series represent the limited number of cosolvents that are both useful and generally acceptable in the formulation of aqueous liquids. Spiegel and Noseworthy, in their review of nonaqueous solvents used in parenteral products, cited a number of solvents that might also be useful in oral liquids.[8] These include glycerol dimethylketal, glycerol formal, glycofurol, dimethylacetamide, N-(β-hydroxyethyl)-lactamide, ethyl lactate, ethyl carbonate, and 1,3-butylene glycol. It should be emphasized, however, that with the possible exception of dimethylacetamide, all of these solvents are unproven with respect to their acceptability for systemic use. Dimethylacetamide has been used as a cosolvent in parenteral products, but its use in oral liquids is seriously limited, owing to the difficulty of masking its objectionable odor and taste. Thus, the spectrum of solvents from which one may make a selection is extremely narrow. Nevertheless, the frequency of their use is high, as can readily be seen by reviewing the formulas for a variety of official and proprietary oral liquids.

Cosolvents are employed not only to effect solubility of the drug, but also to improve the solubility of volatile constituents used to impart a desirable flavor and odor to the product.

Much of the early data on the solubility of pharmaceutical solutes in mixed solvents have been reported as a function of solvent composition; no attempt has been made to explain the data. In recent years, much more emphasis has been placed on cultivating a basic understanding of this phenomenon, with the objective of developing a mathematical approach to interpreting and predicting solubility behavior. Hildebrand and Scott have developed an equation that yields a thermodynamic measure of the cohesive forces that exist within a homogeneous substance.[9,10] This number is often referred to as *Hildebrand's solubility parameter.*

There are several serious limitations to the practical application of the solubility parameter concept to pharmaceutical systems. The approach is restricted to what Hildebrand terms "regular solutions." A regular solution has been defined as one in which there are no interactions between the various solvents present and between the solute and the solvents. All molecules are randomly distributed and oriented in the system. In thermodynamic language, this may be stated as "a solution involving no entropy change when a small amount of one of its components is transferred to it from an ideal solution of the same composition, the total volume remaining unchanged."[10] An additional liability to the solubility parameter approach is the thermodynamic values that must be known to solve the Hildebrand-Scott equation for solubility:

$$\log X_2 = \frac{\Delta Hm^F}{4575}\left(\frac{Tm - T}{TmT}\right) + \frac{\Delta Cp}{4575}\left(\frac{Tm - T}{T}\right) - \frac{\Delta Cp}{1.987}\log\frac{Tm}{T} - \frac{V_2}{4.575T}(\delta_1 - \delta_2)^2\phi_1^2 \qquad (15)$$

where:

X_2 = mole fraction solubility at temperature T

ΔHm^F = heat of fusion of the solute at its melting point Tm

$\Delta Cp = Cp^l - Cp^s$ where Cp^l and Cp^s are the molal heat capacities of the liquid and solid forms

V_2 = molar volume of the solute

δ_1 = solubility parameter of the solvent

δ_2 = solubility parameter of the solute

$$= \left(\frac{\Delta E^V}{V}\right)^{1/2} \text{ or } \left(\frac{\Delta H - RT}{V^l}\right)^{1/2}$$

ϕ_1 = volume fraction of the solvent

Assuming that the solubility parameter values were known for all pharmaceutically useful solvents, the thermodynamic data for each solute of interest would still have to be determined.

Martin and co-workers attempted to use this theory in their study concerning the solubility of benzoic acid in mixed solvent systems.[11,12] The solubility of benzoic acid was found to be in general agreement with the values predicted by the Hildebrand equation, particularly when the solubility parameter of the mixed solvent was approximately equal to the solubility parameter of benzoic acid. The same general conclusions were reached when the solubility of a series of p-hydroxybenzoic acid esters were studied, and the experimental data were compared with the value predicted by the solubility parameter approach. Other authors have extended solubility studies with benzoic acid to other binary and ternary solvent systems.[13]

Dielectric Constant. A more practical, although admittedly less rigorous, approach to the solubility problem may be found in what has come to be known as the "dielectric require-

TABLE 15-3. *Effect of Storage Temperature on Aspartame Stability in Aqueous Solutions at pH 4.0*

Temperature storage (°C)	*Calculated time for 20% decomposition (days)*
10	387
20	134
30	51
40	22
55	5
68	2
80	1
90	0.15

Reprinted with permission from Beck, C.I.: Application potential for aspartame in low calorie and dietetic foods. *In* Low Calorie and Special Dietary Foods: Edited by B.K. Dwivedi. CRC Press, 1978. Copyright CRC Press, Inc., Boca Raton, FL.

Viscosity Control

It is sometimes desirable to increase the viscosity of a liquid, either to serve as an adjunct for palatability or to improve pourability. This can be achieved by increasing the sugar concentration or by incorporating viscosity-controlling agents such as polyvinylpyrrolidone or various cellulosic derivatives (e.g., methylcellulose or sodium carboxymethylcellulose). These compounds form solutions in water that are stable over a wide pH range. Methylcellulose and carboxymethylcellulose are available in a number of different viscosity grades. Carboxymethylcellulose may be used in solutions containing high concentrations of alcohol (up to 50%) without precipitating. It is precipitated, however, as an insoluble salt of a number of multivalent metal ions such as Al^{+++}, Fe^{+++}, and Ca^{++}. Methylcellulose polymers do not form insoluble salts with metal ions, but can be salted out of solution when the concentration of electrolytes or other dissolved materials exceed certain limits. These limits may vary from about 2 to 40%, depending on the electrolyte and the type of methylcellulose involved.

Viscosity-inducing polymers should be used with a degree of caution. They are known to form molecular complexes with a variety of organic and inorganic compounds, and in so doing, influence the activity of these compounds. It is conceivable that highly viscid systems that resist dilution by gastrointestinal fluids might impede drug release and absorption.

Flavors

Flavoring can be divided into two major categories: selection and evaluation. Much has been written on both phases of pharmaceutical flavoring, but selection remains a totally empiric activity.

The four basic taste sensations are salty, bitter, sweet, and sour. Some generalizations concerning the selection of flavors to mask specific types of taste have been suggested by Janovsky,[52] and by Wesley.[53] (See Table 15-4.)

A combination of flavoring agents is usually required to mask these taste sensations effectively. Menthol, chloroform, and various salts frequently are used as flavor adjuncts. Menthol and chloroform are sometimes referred to as *desensitizing agents*. They impart a flavor and odor of their own to the product and have a mild anesthetic effect on the sensory receptor organs associated with taste. Monosodium glutamate has been widely used in the food industry, and to a lesser extent, in pharmaceuticals, for its reported ability to enhance natural flavors. A carefully selected panel reported this substance to be effective in reducing the metallic taste of iron-containing liquids, as well as the bitterness and aftertaste of a variety of other pharmaceutical preparations.[54] It cannot be used in pediatric products, however.

Chemburkar and Joslin have reported that the partitioning of parabens into flavoring oils from aqueous systems depends on the concentration of the flavoring oil, the nature and concentration of the additives, and pH.[55]

Wesley's Pharmaceutical Flavor Guide contains suggestions for flavoring over 51 types of pharmaceutical preparations.[53] It and many similar reports provide some guidance for the formulation chemist, but the final selection

TABLE 15-4. *Flavor Selection*

Taste Sensation	*Recommended Flavor*
Salt	Butterscotch, maple, apricot, peach, vanilla, wintergreen mint
Bitter	Wild cherry, walnut, chocolate, mint combinations, passion fruit, mint spice, anise
Sweet	Fruit and berry, vanilla
Sour	Citrus flavors, licorice, root beer, raspberry

16

Pharmaceutical Suspensions

NAGIN K. PATEL, LLOYD KENNON,* *and* R. SAUL LEVINSON

Suspensions form an important class of pharmaceutical dosage forms. These disperse systems present many formulation, stability, manufacturing, and packaging challenges. The primary objective of this chapter is not to develop a formulary, but rather to put forth some of the basic theoretic and practical considerations that apply to suspension systems, and to relate these principles to formulation methods, evaluation procedures, and manufacturing techniques. The reader is assumed to have at least some knowledge of basic pharmaceutical technology.

For the most part, only aqueous suspensions are discussed, and little attention is paid to oils or aerosol propellants as suspension vehicles. Also, this discussion is limited to suspensions with particles having diameters greater than 0.2 micron, approximately the lower limit of resolution of optical microscopes; for purposes of comparison, a human hair has a diameter of about 75 microns (0.003 in.). Systems with particles smaller than 0.1 to 0.2 micron are generally considered to be colloidal, and they exhibit properties that lie between those of true molecular solutions and suspensions of visible particles. Thus, although suspended particles do not exhibit all the properties of colloids, such as the so-called colligative properties, they do have heightened surface properties, that is, whatever surface properties exist are magnified because of the increased surface area. In actual experience, this additional action expresses itself as an enhanced power of adsorption. The colligative properties just noted depend on the number of "particles" (molecules, ions, aggregates) rather than on their nature. They are possessed by true solutions and by many colloidal solutions and are manifested as freezing-point depression, boiling-point elevation, and osmotic-pressure phenomena.

Suspensions are heterogeneous systems consisting of two phases. The *continuous* or *external phase* is generally a liquid or semisolid, and the *dispersed* or *internal phase* is made up of particulate matter that is essentially insoluble in, but dispersed throughout, the continuous phase; the insoluble matter may be intended for physiologic absorption or for internal or external coating functions. The dispersed phase may consist of discrete particles, or it may be a network of particles resulting from particle-particle interactions. Almost all suspension systems separate on standing. The formulator's main concern, therefore, is not necessarily to try to eliminate separation, but rather to decrease the rate of the settling and to permit easy resuspendability of any settled particulate matter. A satisfactory suspension must remain sufficiently homogeneous for at least the period of time necessary to remove and administer the required dose after shaking its container. Traditionally, certain kinds of pharmaceutical suspensions have been given separate designations, such as mucilages, magmas, gels, and sometimes aerosols; also included would be dry powders to which a vehicle is added at the time of dispensing.

Theoretic Considerations

A knowledge of the theoretic considerations pertaining to suspension technology should ultimately help the formulator to select the ingredients that are most appropriate for the suspension and to use the available mixing and milling equipment to the best advantage. Some understanding of wetting, particle interaction, electrokinetics, aggregation, and sedimentation concepts facilitates the making of good formulatory decisions.

*Deceased

dered settling, and the smallest settle more rapidly. In aggregated suspensions, the particles are linked together into flocs, which initially settle according to the size of the floc and porosity of the aggregated mass. Later, the rate is governed by compaction and rearrangement processes. A clear supernatant is formed on settling, since even the smallest particles are entrapped in the mesh-like network of the floc. Intermediate states are possible in which all particles are not associated with flocs.

As experimental examples, it is noted that Jones, Matthews, and Rhodes studied the stability of sulfaguanidine suspensions as they were affected by electrolyte (aluminum chloride), type and concentration of surfactant (cetyltrimethylammonium bromide, polysorbate 80), and nature of vehicle (water with various amounts of glycerol).[5] They achieved optimum stability by balancing the adjuvants to obtain a controlled aggregation. Also of interest, Carless and Ocran related, in hectorite dispersions, for example, particle shape, particle interaction mediated by added electrolytes, and some rheologic properties.[6] As reported in a patent, Storz,[7] doing research on intramuscular injectables containing steroidal and other water-insoluble medicaments, found that a pharmaceutically elegant, readily redispersible, stable, well-preserved, moderately aggregated suspension would form in an aqueous vehicle having as additives a nonionic polyether surfactant (up to 1% of, for example, polysorbate 80, PEGs, or polyoxyethylenepolyoxypropylene block polymers) and normal preservative concentrations of benzyl alcohol (0.5 to 1.5%) *and* the parabens (0.1 to 0.3%).

To determine whether a suspension is aggregated, a differential manometer can be used to compare the pressure of a suspension near its bottom and top in a container. This device has been described by Tingstad.[8] An aggregated suspension shows the same pressure at both points, as it exerts little or no pressure on the liquid because the particles essentially support each other. A deaggregated suspension, however, exerts more pressure near its bottom.

Caking is defined as the formation of a nonredispersible sediment within a suspension system. The major causes of caking are crystal bridging and closed aggregate (coagule) formation.

In crystal bridging, particle surface crystal growth occurs on two or more particles simultaneously and results in the steady formation of crystal-linked particles, ultimately leading to the formation of a highly linked sediment akin to concrete or plaster. Suspensions of the dispersed type tend to cake easily, owing to the compact sedimentation that occurs when these suspensions settle. Since suspensions are saturated solutions of the particulate substance, small changes in temperature that occur during shelf storage lead to unexpectedly rapid caking via crystal bridging, much in the same way that crystal growth yields can be optimized by alternately warming and cooling a mother crystallization liquor. This process, known as *Ostwald ripening,* is unavoidable in pharmaceutical suspensions of the dispersed type. Caking via crystal bridging can be minimized by utilizing the open network aggregate (floccule) suspension type, as the particles cannot sediment to a close proximity because of the rigidity of the aggregate. From a practical point of view, since fully aggregated suspensions are often unsightly, partial aggregation is often a desired objective, as it leads resistance to caking and imparts esthetic qualities to a suspension formulation.

Caking can also occur by extensive closed aggregate (*coagule*) formation, although the mechanism of nonredispersibility is different in that crystal bridging is not involved. A sedimented, highly coagulated suspension tends to form large coagules as the surface films present on coagulated particles cause the "filmed" particles to cling to each other. Although crystal growth may not occur upon sedimentation because of the presence of the surface films, the end result of a film-bonded sediment that cannot be redispersed is often observed for coagulated suspensions.

Sedimentation Rates

With regard to actual settling rates, the well-known Stokes relation describes the sedimentation velocity of a particle in suspension:

$$v = \frac{2r^2(d_1 - d_2)g}{9\eta} = \frac{D^2(d_1 - d_2)g}{18\eta}$$

where v = velocity of the sedimentation in cm/sec; r = particle radius and D = particle diameter in cm; d_1 and d_2 = density of the particle and the liquid, respectively, in g/ml; g = gravitational constant = 980.7 cm sec^{-2}; and η = the viscosity of the medium in poises, i.e., g cm^{-1} sec^{-1} in cgs units. Note, incidentally, that water at 20° has a viscosity of approximately one centipoise (0.01 poise). The student should be aware of the fact that assumptions were needed to facilitate the derivation of this relationship. Pharmaceutical systems containing

logic characteristics in a pharmaceutical product under development. In particular, the following rheologic characteristics are most undesirable because of their poor physical stability: pseudoplastic (in which there is no yield value), dilatant, and rheopexic (in which viscosity increases with shear force).

Formulation Adjuvants

Certain aspects of suspension formulation pertain to both aggregate and dispersed suspension systems and are therefore discussed together. Suspension adjuvants must be considered. These agents include the preservative, color, perfume, and flavor; they may materially affect the characteristics of the suspension system. In general, most colors are used in small quantities and are usually compatible; flavors and perfumes are similarly used and are also usually compatible with the vehicle. To illustrate that one must be on guard against adjuvant interaction, it is noted that Bean and Dempsey showed that the adsorptive power of kaolin suspensions can reduce the activity of some preservatives.[12] Kaolin hurt the quaternary benzalkonium chloride (BAK), but not the nonionic and less surface-active m-cresol. Similarly, it was shown that procaine penicillin adsorbed the quaternary and that the supernatants of the BAK systems had less activity than the suspensions; thus, the adsorbent acted as a reservoir.

Perhaps the final "adjuvant" one should consider is the package. Usually, initial laboratory screening employs conventional graduates or readily available bottles. When final packaging is considered, it should be noted that various types of glass are available. The types vary with respect to their ability to resist water attack, the degree of attack being related to the amount of alkali released from the glass. The USP should be consulted for further details, as it describes both the tests and standards that should be met by containers to be used for packaging parenteral and nonparenteral (oral or topical) products. One point of terminology may be noted: "flint" refers to clear, colorless, brilliant glass. Originally, it contained lead and was also called "lead" or "crystal" glass; today in commerce, nonlead, highly color-free, soda-lime-silica glasses, the most common general-purpose transparent glasses, are also called flint. Parenteral multiple-dose vials may be "flint" (colorless) or amber, and may be silicone-coated to improve drainage of the suspensions. (Silicone coating also minimizes the leaching of alkali from the glass.) This technique of silicone coating is used widely for suspensions of steroids and combinations of penicillin and dihydrostreptomycin. It is also used in preparations with high solids content, in which formulation modifications cannot measurably improve the drainage of the preparation.

There has been a trend to package suspension systems for oral and topical administration in polyethylene or other plastic containers. Many factors must be considered when a suspension is evaluated in such a container. These factors include loss of flavor and perfume, preservative adsorption, and leaching into the product of substances from the container. Before evaluative procedures are discussed per se, it must be stressed that after the initial stability observations are completed, the determination of the stability of the suspension in the *final package* is an important step of the product development procedure.

Preparative Techniques

The actual preparation of suspensions involves choosing the ingredients (utilizing principles already discussed) and determining the type of manufacturing equipment to be used. Needless to say, each suspension is a separate case and absolute generalization is not possible.

If the suspension is made by a dispersion process, it is best to achieve pulverization of the solid by a micronization technique. This involves subjecting the particles to a turbulent air chamber in which they collide with each other and fracture. Particles under 5 microns are readily obtained. Although it is not widely used for this purpose, spray-drying also can be considered a method of comminution to produce a finely divided solid phase.

If the suspension is made by controlled crystallization, a supersaturated solution should be formed and then quickly cooled with rapid stirring. This causes the formation of many nuclei and hence many crystals; it is just the opposite of letting crystals grow large.

At some time during suspension formation, it is likely that shearing will be desired. This homogenization can be accomplished by the conventional stator-rotor colloid mills. Ultrasonic equipment also can be used to effect high intensity mixing, but usually, this technique is not applied commercially. Of interest, however, is the work of Sheikh, Price, and Gerraughty, who studied the effect of ultrasound on polyethylene spheres in aqueous suspension.[13] The ultrasound reduced the sphere size only when surfactants were added, especially those having high HLBs. When such agents were used as

additives, the particles were readily dispersed and hence completely surrounded by liquid. Since ultrasound waves and cavitation shock waves are transmitted to the particles through the liquid medium, a poor suspension would not be as susceptible to size reduction as a better dispersed one. Excessive shearing (or high temperatures) may irreversibly damage polymeric materials such as gums, so that viscosity loss is suffered. Instead of trying to hydrate gums and clays by massive shearing, it is often better, when possible, to give the material the necessary time to hydrate under conditions of mild shearing. An alternate procedure is to mix with, or preferably spray the gum with, a chlorinated hydrocarbon, acetone, or alcohol solution of a wetting agent (e.g., sodium dioctyl sulfosuccinate). About 0.4% (based on the gum weight) of the wetting agent should be added to the gum. This technique can produce a marked beneficial effect, as wetting of the gum and hence hydration is greatly accelerated.

A final comment is that processing studies in a pilot plant are needed because it is axiomatic that the scale-up operation from laboratory batches to production lots brings with it many troubles and unexpected results.

Evaluation of Suspension Stability

Since stability testing is discussed elsewhere in the pharmaceutical literature, the only emphasis here is on the most pertinent aspects of suspension stability. Techniques for the evaluation of heterogeneous systems generally are complex and are far from being completely satisfactory. Some test methods are so drastic that the stability information is obtained during an evaluation that destroys the system being evaluated. Some methods are somewhat empiric in nature, i.e., the exact basis on which they operate cannot be explicitly defined mathematically. All test procedures suffer some limitations, and the results, therefore, must be cautiously evaluated and interpreted. As the methodology involved in the pertinent stability studies is often somewhat complicated, this section of the chapter is more fully referenced so that further details can be obtained if desired. The purpose here is to point out explicitly one method, and then indicate only the general nature of some of the other approaches taken. Use of evaluation techniques permits the formulator to screen the initial preparations made and also to compare the improved formulations to competitive commercial products. The latter point should not be treated lightly even though it does not deal with absolute standards.

Sedimentation Volume

Since redispersibility is one of the major considerations in assessing the acceptability of a suspension, and since the sediment formed should be easily dispersed by moderate shaking to yield a homogeneous system, measurement of the sedimentation volume and its ease of redispersion form two of the most common basic evaluative procedures.

The concept of sedimentation volume is simple. In short, it considers the ratio of the ultimate height (H_u) of the sediment to the initial height (H_o) of the total suspension as the suspension settles in a cylinder under standard conditions. The larger this fraction, the better is the suspendability.

Methods utilizing the sedimentation volume obtained in a cylinder offer a practical approach to the determination of the physical stability of suspension systems. Particularly good is the fact that the system remains undisturbed. Specifically, it is worth knowing how to use the H_u and H_o concepts. The formulator should obtain the H_u/H_o ratios and plot them as ordinates with time as the abscissae. Note that although the conventional H_u is called the "ultimate" height of the sediment, ultimate really means the height at any particular time. The plot just described will at time zero start at 1.0, with the curve then being either horizontal or gradually sloping downward to the right as time goes on. One can compare different formulations and choose the best by observing the lines, the better formulations obviously producing lines that are more horizontal and/or less steep. Another technique that utilizes essentially the same parameters may be used to evaluate highly concentrated suspensions, which might be difficult to compare because there would be only minimum supernatant liquid. The technique involves diluting the suspension with additional vehicle, i.e., with the total formula with all ingredients except the insoluble phase. As an example, one could dilute 50 ml of a suspension to a volume of 100, 150, or 200 ml. The H_u reading then becomes the volume of sediment in the diluted sample, and H_o equals the original volume of the sample before dilution. The H_u/H_o ratio may in this case be greater than 1. Regardless, the ratio is again plotted against time, and comparisons between formulas are made as before.

One additional concept should also be considered by the formulator. In all the comparisons

ally, to provide slow, constant, and sustained release of a drug over a prolonged period of time, essentially to simulate and replace the more hazardous, continuous intravenous infusion of a drug. Rarely, if ever, is the ideal achieved, but extensive research has resulted in depot dosage forms that approach the desired goal.

In one type of depot formulation, which is referred to as "dissolution-controlled," the rate of drug absorption is controlled by the slow dissolution of drug particles, with subsequent release to tissue fluid surrounding the bolus of product in the tissue. The formation of drug salts with very low aqueous solubility is one of the most common approaches to this type of formulation. Control of the particle size also can contribute to slow dissolution in that larger particles or crystals dissolve more slowly than small crystals with proportionately more surface area. Further, the suspension of the drug particles in vegetable oils, and especially if gelled with substances such as aluminum monostearate, produces prolonged absorption rates.

Another type of depot formulation is produced by the binding of drug molecules to adsorbents. Only the free portion, in equilibrium with that which is bound, can be absorbed. As drug is absorbed, a shift in equilibrium is established, and the drug is slowly released from the bound state to the free state. This is particularly exemplified by the binding of vaccines to aluminum hydroxide gel to provide a sustained release. A third type of depot preparation is the encapsulation type, in which biodegradable or bioabsorbable macromolecules such as gelatin, phospholipids, and long-chain fatty acids become a diffusion matrix for the drug. The drug is encapsulated within the matrix, and release of drug molecules is controlled by the rate of permeation out of the diffusion barrier and by the rate of biodegradation of the barrier macromolecules. A fourth type is the esterification type depot preparation, in which esters of a drug that are bioerodible are synthesized. The esterified drug is deposited in tissue at the site of injection to form a reservoir of drug. The rate of drug absorption is controlled by the partitioning of the drug esters from the reservoir to tissue fluid and by the rate at which the drug ester regenerates the active drug molecule. Often, these esters are dissolved or suspended in oleaginous vehicles, which further slow the release.

Long-acting parenteral drug formulations have been extensively reviewed in an article by Chien,[60] which should be consulted for more details of this important type of dosage form.

Suspensions. The solids content of parenteral suspensions usually ranges between 0.5 and 5%, but may go as high as 30% in some antibiotic preparations. The amount of solids and the nature of the vehicle determine the viscosity of the product, an important factor because of syringeability, the facility with which the product is passed in and out of a syringe. The property of thixotropy is sometimes utilized, particularly with oleaginous suspensions, to provide the sedimentation stability of a gelled preparation during storage and the syringeability of a fluid at the time of administration.

Probably the most important requirement for parenteral suspensions is a small and uniform particle size.[61] Various techniques are available for the reduction of particles, including dry or wet ball milling, micropulverization, fluid energy grinding, ultrasonic insonation of shock-cooled saturated solutions, and spray drying. Small, uniform particles are required to give slow, uniform rates of sedimentation and predictable rates of dissolution and drug release. Also, uniform particle size reduces the tendency for larger crystal growth during storage, since it has been found that relatively small crystals often tend to disappear and large crystals grow larger in a mixture. Such a change can cause caking of a suspension, difficult syringeability because of the large particles and changes in the dissolution and drug release rate following injection.

The stabilization of a suspension for the period between manufacture and use presents a number of problems. As indicated, solids gradually settle and may cake, causing difficulty in redispersion prior to use. Surface active agents may aid in the preparation and stabilization of a suspension by reducing the interfacial tension between the particles and the vehicle. Polysorbate 80, lecithin, Emulphor EL-620* and Pluronic F-68† are among the surface active agents that have been used in parenteral suspensions. The concurrent addition of a hydrocolloid, such as sodium carboxymethylcellulose, may enhance the effect of the surfactant and cause loss of surface charge of the dispersed particles, water repellency, and the tendency to agglomerate.[62] The following is an example of such a formulation:

Cortisone acetate, microfine	25 mg
Polysorbate 80 (surface active agent)	4 mg
Sodium CMC (protective colloid)	5 mg
Sodium chloride (for tonicity effect)	9 mg
Benzyl alcohol (antibacterial)	9 mg
Water for Injection, to make	1 ml

*GAF Corp., New York, NY 10020.
†Wyandotte Chemicals Corp., Wyandotte, MI 48192.

Among other protective colloids that have been employed are acacia, gelatin, methylcellulose, and polyvinylpyrrolidone.

Occasionally, parenteral suspensions may be improved by a slight increase in viscosity, either by increasing the amount of protective colloid or by adding a compound such as sorbitol. In other formulations, it has been found that flocculation of the suspended particles has been necessary to prevent packing to a dense cake. The addition of selected ions that increase the surface charge of the solid particles may cause them to form fluffy aggregates. These settle rapidly, but to a large sedimentation volume, which can easily be redispersed. Monosodium citrate has been used effectively for such a purpose.

Emulsions. The principal problem in the formulation of parenteral emulsions is the attainment and maintenance of uniform oil droplets of 1 to 5 microns in size as the internal phase. With emulsions, separation of the phase does not occur as readily as with suspensions because the difference in density between the oil and water is relatively small. One such product, an emulsion of a natural vitamin K_1, has been stabilized with lecithin.

Intravenous nutrient emulsions that have been made contain, for example, 15% cottonseed oil, 4% dextrose, 1.2% lecithin, and 0.3% of an oxyethyleneoxypropylene polymer, the latter two ingredients being the emulsifiers. The dispersed phase should have droplet sizes of less than 1 micron. The emulsion must be stable to autoclaving. Elevated temperatures, however, tend to produce coalescence of the dispersed phase, and excessive shaking has caused acceleration of the rate of creaming. Small amounts of gelatin, dextran, and methylcellulose have been found to aid in stabilizing the emulsions, but they are also adversely affected by elevated temperatures.

The preparation of a parenteral emulsion is troublesome. It is made more difficult by the rigid requirement for particle size control to prevent emboli in blood vessels, by the limited choice of emulsifiers and stabilizers of low toxicity, and by the preservation of the oil phase against the development of rancidity.

Effect of Route of Administration. Parenteral preparations may be given by several routes.[63] The five most common are intravenous, intramuscular, subcutaneous, intracutaneous, and intraspinal.

The intended route of administration has a marked effect on the formulation of a parenteral product. The volume in which a dose of the drug must be encompassed is one factor to consider. For intracutaneous injections a volume of more than 0.2 ml rarely is used because tissue volume is small and compact; also, absorption is quite slow owing to the lack of blood vessels. Volumes of 1 ml or less may be injected subcutaneously, and only occasionally are volumes of more than 2 ml given intramuscularly. Volumes of 10 ml or less may be given intraspinally, but only by the intravenous route may large volumes be given safely, provided careful control of the rate of administration is undertaken. It is not convenient to administer a volume of more than 20 ml by a syringe, and usually it is not practical to set up an infusion unit for less than 250 ml.

Isotonicity is a characteristic that is probably of greatest importance for intraspinal injections because the circulation of the cerebrospinal fluid is slow, and disturbances of osmotic pressure quickly cause headache and vomiting. Since intracutaneous injections are given mostly for diagnostic purposes, nonisotonic solutions may cause false signs of irritation. Isotonicity is preferable for the comfort of the patient, but is not essential for subcutaneous and intramuscular injections. For the rapid absorption of drugs given intramuscularly, a slightly hypertonic solution may increase the rate by causing local effusion of tissue fluids. Usually, intravenous fluids should be isotonic, although slow administration of a paratonic solution may be performed safely if rapid dilution with the blood occurs.

In general, only solutions of drugs in water may be given intravenously. Suspensions may not be given because of the danger of blockage of the small blood vessels. Aqueous or oleaginous suspensions and oleaginous solutions cannot normally be given subcutaneously because of the pain and irritation caused. Muscle tissue tolerates oils and suspended particles fairly well and is therefore the only route normally suitable for their administration.

The administration of a drug deep into the muscle tissue results in a pool of the product at the site of injection. From this depot, the drug is released at a rate determined to a large extent by the characteristics of the formulation. Whether the solvent is aqueous or oleaginous affects the rate of absorption; oleaginous solutions are usually more slowly absorbed. Increasing the viscosity of solutions slows the absorption, as do gelatin or polyvinylpyrrolidone in water and aluminum monostearate in oils. Utilizing modifications of the drug molecule to render it less soluble (for instance, the formation of various esters or salts) permits the production of stable suspensions, causing a marked reduction in the rate of absorption of the drug from the depot. Thus, utilizing various modifications in formulation of