Remington: The Science and Practice of Pharmacy

Nineteenth Edition

Volume II

Remington: The Science and Practice of Pharmacy

Volume II

19TH EDITION

Remington: Practice of

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Chairman of the Editorial Board and Editor

The Science and Pharmacy

1995

MACK PUBLISHING COMPANY
Easton, Pennsylvania 18042

CHAPTER 92

Oral Solid Dosage Forms

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Drug substances most frequently are administered orally by means of solid dosage forms such as tablets and capsules. Large-scale production methods used for their preparation, as described later in the chapter, require the presence of other materials in addition to the active ingredients. Additives also may be included in the formulations to facilitate handling, enhance the physical appearance, improve stability and aid in the delivery of the drug to the bloodstream after administration. These supposedly inert ingredients, as well as the production methods employed, have been shown in some cases to influence the absorption or bioavailability of the drug substances.[1] Therefore, care must be taken in the selection and evaluation of additives and preparation methods to ensure that the drug-delivery goals and therapeutic efficacy of the active ingredient will not be diminished.

In a limited number of cases it has been shown that the drug substance's solubility and other physicochemical characteristics have influenced its physiological availability from a solid dosage form. These characteristics include its particle size, whether it is amorphous or crystalline, whether it is solvated or nonsolvated and its polymorphic form. After clinically effective formulations are obtained, such variations among dosage units of a given batch, as well as batch-to-batch differences, should be reduced to a minimum through proper in-process controls and good manufacturing practices. The recognition of the importance of validation both for equipment and processes greatly has enhanced assurance in the reproducibility of formulations. It is in these areas that significant progress has been made with the realization that large-scale production of a satisfactory tablet or capsule depends not only on the availability of a clinically effective formulation but also on the raw materials, facilities, personnel, documentation, validated processes and equipment, packaging and the controls used during and after preparation (Fig 1).

Fig 1. Tablet press operators checking batch record in conformance with Current Good Manufacturing Practices (courtesy, Lilly).

Tablets

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or molding methods. They have been in widespread use since the latter part of the 19th century and their popularity continues. The term *compressed tablet* is believed to have been used first by John Wyeth and Brother of Philadelphia. During this same period, molded tablets were introduced to be used as *hypodermic* tablets for the extemporaneous preparation of solutions for injection. Tablets remain popular as a dosage form because of the advantages afforded both to the manufacturer (eg, simplicity and economy of preparation, stability and convenience in packaging, shipping and dispensing) and the patient (eg, accuracy of dosage, compactness, portability, blandness of taste and ease of administration).

Although the basic mechanical approach for their manufacture has remained the same, tablet technology has undergone great improvement. Efforts are being made continually to understand more clearly the physical characteristics of powder compaction and the factors affecting the availability of the drug substance from the dosage form after oral administration. Tableting equipment continues to improve both as to production speed and the uniformity of tablets compressed. Recent advances in tablet technology have been reviewed.[2–13]

Although tablets frequently are discoid in shape, they also may be round, oval, oblong, cylindrical or triangular. They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration. They are divided into two general classes, whether they are made by compression or molding. Compressed tablets usually are prepared by large-scale production methods, while molded tablets generally involve small-scale operations. The various tablet types and abbreviations used in referring to them are listed below.

Compressed Tablets (CT)

These tablets are formed by compression and contain no special coating. They are made from powdered, crystalline or granular materials, alone or in combination with binders, disintegrants, controlled-release polymers, lubricants, diluents and, in many cases, colorants.

Sugar-Coated Tablets (SCT)—These are compressed tablets containing a sugar coating. Such coatings may be colored and are beneficial in covering up drug substances possessing objectionable tastes or odors, and in protecting materials sensitive to oxidation.

Film-Coated Tablets (FCT)—These are compressed tablets which are covered with a thin layer or film of a water-soluble material. A number of polymeric substances with film-forming properties may be used. Film coating imparts the same general characteristics as sugar coating with the added advantage of a greatly reduced time period required for the coating operation.

Enteric-Coated Tablets (ECT)—These are compressed tablets coated with substances that resist solution in gastric fluid but disintegrate in the intestine. Enteric coatings can be used for tablets containing drug substances which are inactivated or destroyed in the stomach, for those which irritate the mucosa or as a means of delayed release of the medication.

Multiple Compressed Tablets (MCT)—These are compressed tablets made by more than one compression cycle.

Layered Tablets—Such tablets are prepared by compressing additional tablet granulation on a previously compressed granulation. The operation may be repeated to produce multilayered tablets of two or three layers. Special tablet presses are required to make layered tablets such as the Versa press (*Stokes / Pennwalt*).

Press-Coated Tablets—Such tablets, also referred to as dry-coated, are prepared by feeding previously compressed tablets into a special tableting machine and compressing another granulation layer around the preformed tablets. They have all the advantages of compressed tablets, ie, slotting, monogramming, speed of disintegration, etc, while retaining the attributes of sugar-coated tablets in masking the taste of the drug substance in the core tablets. An example of a press-coated tablet press is the *Manesty* Drycota. Press-coated tablets also can be used to separate incompatible drug substances; in addition, they can provide a means to give an enteric coating to the core tablets. Both types of multiple-compressed tablets have been used widely in the design of prolonged-action dosage forms.

Controlled-Release Tablets—Compressed tablets can be formulated to release the drug slowly over a prolonged period of time. Hence, these dosage forms have been referred to as *Prolonged-Release* or *Sustained-Release* dosage forms as well. These tablets (as well as capsule versions) can be categorized into three types: (1) those which respond to some physiological condition to release the drug, such as enteric coatings; (2) those that release the drug in a relatively steady, controlled manner and (3) those that combine combinations of mechanisms to release "pulses" of drug, such as repeat-action tablets. The performance of these systems are described in more detail in Chapter 94.

Tablets for Solution—Compressed tablets to be used for preparing solutions or imparting given characteristics to solutions must be labeled to indicate that they are not to be swallowed. Examples of these tablets are Halazone Tablets for Solution and Potassium Permanganate Tablets for Solution.

Effervescent Tablets—In addition to the drug substance, these tablets contain sodium bicarbonate and an organic acid such as tartaric or citric acid. In the presence of water, these additives react liberating carbon dioxide, which acts as a distintegrator and produces effervescence. Except for small quantities of lubricants present, effervescent tablets are soluble.

Compressed Suppositories or Inserts—Occasionally, vaginal suppositories, such as Metronidazole Tablets, are prepared by compression. Tablets for this use usually contain lactose as the diluent. In this case, as well as for any tablet intended for administration other than by swallowing, the label must indicate the manner in which it is to be used.

Buccal and Sublingual Tablets—These are small, flat, oval tablets. Tablets intended for buccal administration by inserting into the buccal pouch may dissolve or erode slowly; therefore, they are formulated and compressed with sufficient pressure to give a hard tablet. Progesterone Tablets may be administered in this way.

Some newer approaches use tablets that melt at body temperature. The matrix of the tablet is solidified while the drug is in solution. After melting, the drug is automatically in solution and available for absorption, thus eliminating dissolution as a rate-limiting step in the absorption of poorly soluble compounds. Sublingual tablets, such as those containing nitroglycerin, isoproterenol hydrochloride or erythrityl tetranitrate, are placed under the tongue. Sublingual tablets dissolve rapidly and the drug substances are absorbed readily by this form of administration.

Molded Tablets or Tablet Triturates (TT)

Tablet triturates usually are made from moist material using a trituration mold which gives them the shape of cut sections of a cylinder. Such tablets must be completely and rapidly soluble. The problem arising from compression of these tablets is the failure to find a lubricant that is completely water soluble.

Dispensing Tablets (DT)—These tablets provide a convenient quantity of potent drug that can be incorporated readily into powders and liquids, thus circumventing the necessity to weigh small quantities. These tablets are supplied primarily as a convenience for extemporaneous compounding and should never be dispensed as a dosage form.

Hypodermic Tablets (HT)—Hypodermic tablets are soft, readily soluble tablets and originally were used for the preparation of solutions to be injected. Since stable parenteral solutions are now available for most drug substances, there is no justification for the use of hypodermic tablets for injection. Their use in this manner should be discouraged since the resulting solutions are not sterile. Large quantities of these tablets continue to be made, but for oral administration. No hypodermic tablets ever have been recognized by the official compendia.

Compressed Tablets (CT)

In order for medicinal substances, with or without diluents, to be made into solid dosage forms with pressure, using available equipment, it is necessary that the material, either in crystalline or powdered form, possess a number of physical characteristics. These characteristics include the ability to flow freely, cohesiveness and lubrication. The ingredients such as disintegrants designed to break the tablet up in gastrointestinal fluids, and controlled-release polymers designed to slow down drug release, ideally should possess these characteristics, or not interfere with the desirable performance traits of the other excipients. Since most materials have none or only some of these properties, methods of tablet formulation and preparation have been developed to impart these desirable characteristics to the material which is to be compressed into tablets.

The basic mechanical unit in all tablet-compression equipment includes a lower punch which fits into a die from the bottom and an upper punch, having a head of the same shape and dimensions, which enters the die cavity from the top after the tableting material fills the die cavity (see Fig 2). The tablet is formed by pressure applied on the punches and subsequently is ejected from the die. The weight of the tablet is determined by the volume of the material which fills the die cavity. Therefore, the ability of the granulation to flow freely into the die is important in insuring a uniform fill, as well as the continuous movement of the granulation from the source of supply or feed hopper. If the tablet granulation does not possess cohesive properties, the tablet after compression will crumble and fall apart on handling. As the punches must move freely within the die and the tablet must be ejected readily from the punch faces, the material must have a degree of lubrication to minimize friction and allow for the removal of the compressed tablets.

There are three general methods of tablet preparation: the wet-granulation method, the dry-granulation method and di-

Fig 2. Basic mechanical unit for tabet compression: lower punch, die and upper punch (courtesy, Vector/Colton).

rect compression. The method of preparation and the added ingredients are selected in order to give the tablet formulation the desirable physical characteristics allowing the rapid compression of tablets. After compression, the tablets must have a number of additional attributes such as appearance, hardness, disintegration ability, appropriate dissolution characteristics and uniformity which also are influenced both by the method of preparation and by the added materials present in the formulation. In the preparation of compressed tablets, the formulator also must be cognizant of the effect which the ingredients and methods of preparation may have on the availability of the active ingredients and, hence, the therapeutic efficacy of the dosage form. In response to a request by physicians to change a dicumarol tablet in order that it might be broken more easily, a Canadian company reformulated to make a large tablet with a score. Subsequent use of the tablet, containing the same amount of drug substance as the previous tablet, resulted in complaints that larger-than-usual doses were needed to produce the same therapeutic response. On the other hand, literature reports indicate that the reformulation of a commercial digoxin tablet resulted in a tablet, although containing the same quantity of drug substance, that gave the desired clinical response at half its original dose. Methods and principles that can be used to assess the effects of excipients and additives on drug absorption have been reviewed.[2,14,15] See Chapters 35, 42 and 83.

Tablet Ingredients

In addition to the active or therapeutic ingredient, tablets contain a number of inert materials. The latter are known as additives or *excipients*. They may be classified according to the part they play in the finished tablet. The first group contains those which help to impart satisfactory processing and compression characteristics to the formulation. These include diluents, binders, glidants and lubricants. The second group of added substances helps to give additional desirable physical characteristics to the finished tablet. Included in this group are disintegrants, colors, and in the case of chewable tablets, flavors and sweetening agents, and in the case of controlled-release tablets, polymers or waxes or other solubility-retarding materials.

Although the term *inert* has been applied to these added materials, it is becoming increasingly apparent that there is an important relationship between the properties of the excipients and the dosage forms containing them. Preformulation studies demonstrate their influence on stability, bioavailability and the processes by which the dosage forms are prepared. The need for acquiring more information and use standards for excipients has been recognized in a joint venture of the Academy of Pharmaceutical Sciences and the Council of the Pharmaceutical Society of Great Britain. The result is called the *Handbook of Pharmaceutical Excipients*. This reference now is distributed widely throughout the world.[16]

Diluents

Frequently, the single dose of the active ingredient is small and an inert substance is added to increase the bulk in order to make the tablet a practical size for compression. Commpressed tablets of dexamethasone contain 0.75 mg steroid per tablet; hence, it is obvious that another material must be added to make tableting possible. Diluents used for this purpose include dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such tablets commonly are called *chewable tablets*. Upon chewing, properly prepared tablets will disintegrate smoothly at a satisfactory rate, have a pleasant taste and feel and leave no unpleasant aftertaste in the mouth. Diluents used as excipients for direct compression formulas have been subjected to prior processing to give them flowability and compressibility. These are discussed under *Direct Compression*, page 1626.

Most formulators of immediate-release tablets tend to use consistently only one or two diluents selected from the above group in their tablet formulations. Usually, these have been selected on the basis of experience and cost factors. However, in the formulation of new therapeutic agents, the compatibility of the diluents with the drug must be considered, eg, calcium salts used as diluents for the broad-spectrum antibiotic tetracycline have been shown to interfere with the drug's absorption from the gastrointestinal tract. When drug substances have low water solubility, it is recommended that water-soluble diluents be used to avoid possible bioavailability problems. Highly adsorbent substances, eg, bentonite and kaolin, are to be avoided in making tablets of drugs used clinically in small dosage, such as the cardiac glycosides, alkaloids and the synthetic estrogens. These drug substances may be adsorbed after administration. The combination of amine bases with lactose, or amine salts with lactose in the presence of an alkaline lubricant, results in tablets which discolor on aging.

Microcrystalline cellulose (Avicel) usually is used as an excipient in direct-compression formulas. However, its presence in 5 to 15% concentrations in wet granulations has been shown to be beneficial in the granulation and drying processes in minimizing case-hardening of the tablets and in reducing tablet mottling.

Many ingredients are used for several different purposes, even within the same formulation; eg, corn starch can be used in paste form as a binder. When added in drug or suspension form, it is a good disintegrant. Even though these two uses are to achieve opposite goals, some tablet formulas use corn starch in both ways. In some controlled-release formulas, the polymer hydroxypropylmethylcellulose (HPMC) is used both as an aid to prolong the release from the tablet, as well as a film-former in the tablet coating. Therefore, most excipients used in formulating tablets and capsules have many uses, and a thorough understanding of their properties and limitations is necessary in order to use them rationally.

Binders

Agents used to impart cohesive qualities to the powdered material are referred to as binders or granulators. They impart a cohesiveness to the tablet formulation which insures the tablet remaining intact after compression, as well as improving the free-flowing qualities by the formulation of granules of desired hardness and size. Materials commonly used as binders include starch, gelatin and sugars as sucrose, glucose, dextrose, molasses and lactose. Natural and synthetic gums which have been used include acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, Veegum and larch arabogalactan. Other agents which may be considered binders under certain circumstances are polyethylene glycol, ethylcellulose, waxes, water and alcohol.

The quantity of binder used has considerable influence on the characteristics of the compressed tablets. The use of too much binder or too strong a binder will make a hard tablet which will not disintegrate easily and which will cause excessive wear of punches and dies. Differences in binders used for CT Tolbutamide resulted in differences in hypoglycemic effects observed clinically. Materials which have no cohesive qualities of their own will require a stronger binder than those with these qualities. Alcohol and water are not binders in the true sense of the word, but because of their solvent action on some ingredients such as lactose, starch and celluloses, they change the powdered material to granules and the residual moisture retained enables the materials to adhere together when compressed.

Binders are used both as a solution and in a dry form depending on the other ingredients in the formulation and the method of preparation. However, several *pregelatinized*

starches available are intended to be added in the dry form so that water alone can be used as the granulating solution. The same amount of binder in solution will be more effective than if it were dispersed in a dry form and moistened with the solvent. By the latter procedure, the binding agent is not as effective in reaching and wetting each of the particles within the mass of powders. Each of the particles in a powder blend has a coating of adsorbed air on its surface, and it is this film which must be penetrated before the powders can be wetted by the binder solution. After wetting, a certain period of time is necessary to dissolve the binder completely and make it completely available for use. Since powders differ with respect to the ease with which they can be wetted, and their rate of solubilization, it is preferable to incorporate the binding agent in solution. By this technique it often is possible to gain effective binding with a lower concentration of binder.

The direct-compression method for preparing tablets (see page 1630) requires a material that not only is free-flowing but also sufficiently cohesive to act as a binder. This use has been described for a number of materials including microcrystalline cellulose, microcrystalline dextrose, amylose and polyvinylpyrrolidone. It has been postulated that microcrystalline cellulose is a special form of cellulose fibril in which the individual crystallites are held together largely by hydrogen bonding. The disintegration of tablets containing the cellulose occurs by breaking the intercrystallite bonds by the disintegrating medium.

Starch Paste—Corn starch is used widely as a binder. The concentration may vary from 10 to 20%. It usually is prepared as it is to be used by dispersing corn starch in sufficient cold purified water to make a 5 to 10% *w/w* suspension and warming in a water bath with continuous stirring until a translucent paste forms. It has been observed that during paste formation, not all of the starch is hydrolyzed. Starch paste then, is not only useful as a binder, but also as a method to incorporate some disintegrant inside the granules.

Gelatin Solution—Gelatin generally is used as a 10 to 20% solution; gelatin solutions should be prepared freshly as needed and used while warm or they will solidify. The gelatin is added to cold purified water and allowed to stand until it is hydrated. It then is warmed in a water bath to dissolve the gelatin, and the solution is made up to the final volume on a weight basis to give the concentration desired.

Cellulosic Solutions—Various cellulosics have been used as binders in solution form. Hydroxypropylmethylcellulose (HPMC) has been used widely in this regard. Typical of a number of cellulosics, HPMC is more soluble in cold water than hot. It also is more dispersable in hot water than cold. Hence, in order to obtain a good, smooth gel that is free from lumps or "fisheyes," it is necessary to add the HPMC in hot, almost boiling water and, under agitation, cool the mixture down as quickly as possible, as low as possible. Other water-soluble cellulosics such as hydroxyethylcellulose (HEC) and hydroxypropylcellulose (HPC) have been used successfully in solution as binders.

Not all cellulosics are soluble in water. Ethylcellulose can be used effectively when dissolved in alcohol, or as a dry binder which then is wetted with alcohol. It is used as a binder for materials that are moisture-sensitive.

Polyvinylpyrrolidone—PVP can be used as an aqueous or alcoholic solution and this versatility has increased its popularity. Concentrations range from 2% and vary considerably.

It will be noted that binder solutions usually are made up to weight rather than volume. This is to enable the formulator to determine the weight of the solids which have been added to the tablet granulation in the binding solution. This becomes part of the total weight of the granulation and must be taken into consideration in determining the weight of the compressed tablet, which will contain the stated amount of the therapeutic agent.

As can be seen by the list of binders in this chapter, most modern binders used in solution are polymeric in form. Because of this, the flow or spreadability of these solutions becomes important when selecting the appropriate granulating equipment. The rheology of polymeric solutions is a fascinating subject in and of itself, and should be considered for these materials.

Lubricants

Lubricants have a number of functions in tablet manufacture. They prevent adhesion of the tablet material to the surfaces of the dies and punches, reduce interparticle friction, facilitate the ejection of the tablets from the die cavity and may improve the rate of flow of the tablet granulation. Commonly used lubricants include talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils and polyethylene glycol (PEG). Most lubricants, with the exception of talc, are used in concentrations less than 1%. When used alone, talc may require concentrations as high as 5%. Lubricants are in most cases hydrophobic materials. Poor selection or excessive amounts can result in "waterproofing" the tablets, resulting in poor tablet disintegration and/or delayed dissolution of the drug substance.

The addition of the proper lubricant is highly desirable if the material to be tableted tends to stick to the punches and dies. Immediately after compression, most tablets have the tendency to expand and will bind and stick to the side of the die. The choice of the proper lubricant effectively will overcome this.

The method of adding a lubricant to a granulation is important if the material is to perform its function satisfactorily. The lubricant should be divided finely by passing it through a 60- to 100-mesh nylon cloth onto the granulation. In production this is called *bolting* the lubricant. After adding the lubricant, the granulation is tumbled or mixed gently to distribute the lubricant without coating the particles too well or breaking them down to finer particles. Some research has concluded that the order of mixing of lubricants and other excipients can have a profound effect on the performance of the final dosage form. Thus, attention to the mixing process itself is just as important as the selection of lubricant materials.

These process variables can be seen in the prolonged blending of a lubricant in a granulation. Overblending materially can affect the hardness, disintegration time and dissolution performance for the resultant tablets.

The quantity of lubricant varies, being as low as 0.1%, and in some cases as high as 5%. Lubricants have been added to the granulating agents in the form of suspensions or emulsions. This technique serves to reduce the number of operational procedures and thus reduce the processing time.

In selecting a lubricant, proper attention must be given to its compatibility with the drug agent. Perhaps the most widely investigated drug is acetylsalicylic acid. Different talcs varied significantly the stability of aspirin. Talc with a high calcium content and a high loss on ignition was associated with increased aspirin decomposition. From a stability standpoint, the relative acceptability of tablet lubricants for combination with aspirin was found to decrease in the following order: hydrogenated vegetable oil, stearic acid, talc and aluminum stearate.

The primary problem in the preparation of a water-soluble tablet is the selection of a satisfactory lubricant. Soluble lubricants reported to be effective include sodium benzoate, a mixture of sodium benzoate and sodium acetate, sodium chloride, leucine and Carbowax 4000. However, it has been suggested that formulations used to prepare water-soluble tablets may represent a number of compromises between compression efficiency and water solubility. While magnesium stearate is one of the most widely used lubricants, its hydrophobic properties can retard disintegration and dissolution. To overcome these waterproofing characteristics, sodium lauryl sulfate sometimes is included. One compound found to have the lubricating properties of magnesium stearate without its disadvantages is magnesium lauryl sulfate. Its safety for use in pharmaceuticals has not been established.

Glidants

A glidant is a substance which improves the flow characteristics of a powder mixture. These materials always are added in the dry state just prior to compression (ie, during the lubrication step). Colloidal silicon dioxide [Cab-o-sil (*Cabot*)] is the most commonly used glidant and generally is used in low concentrations of 1% or less. Talc (asbestos-free) also is used and may serve the dual purpose as lubricant/glidant.

It is especially important to optimize the order of addition and the mixing process for these materials in order to maximize their effect and to make sure that their influence on the lubricant(s) is minimized.

Disintegrants

A disintegrant is a substance, or a mixture of substances, added to a tablet to facilitate its breakup or disintegration after administration. The active ingredient must be released from the tablet matrix as efficiently as possible to allow for its rapid dissolution. Materials serving as disintegrants have been classified chemically as starches, clays, celluloses, algins, gums and cross-linked polymers.

The oldest and still the most popular disintegrants are corn and potato starch which have been well-dried and powdered. Starch has a great affinity for water and swells when moistened, thus facilitating the rupture of the tablet matrix. However, others have suggested that its disintegrating action in tablets is due to capillary action rather than swelling; the spherical shape of the starch grains increases the porosity of the tablet, thus promoting capillary action. Starch, 5%, is suggested, but if more rapid disintegration is desired, this amount may be increased to 10 or 15%. Although it might be expected that disintegration time would decrease as the percentage of starch in the tablet increased, this does not appear to be the case for tolbutamide tablets. In this instance, there appears to be a critical starch concentration for different granulations of the chemical. When their disintegration effect is desired, starches are added to the powder blends in the dry state.

A group of materials known as *super disintegrants* have gained in popularity as disintegrating agents. The name comes from the low levels (2 to 4%) at which they are completely effective. Croscarmelose, crospovidone and sodium starch glycolate represent examples of a cross-linked cellulose, a cross-linked polymer and a cross-linked starch, respectively.

The development of these disintegrants fostered new theories about the various mechanisms by which disintegrants work. Sodium starch glycolate swells 7- to 12-fold in less than 30 seconds. Croscarmelose swells 4- to 8-fold in less than 10 seconds. The starch swells equally in all three dimensions, while the cellulose swells only in two dimensions, leaving fiber length essentially the same. Since croscarmelose is the more efficient disintegrating agent, it is postulated that the rate, force and extent of swelling play an important role in those disintegrants that work by swelling. Cross-linked PVP swells little, but returns to its original boundaries quickly after compression. Wicking, or capillary action, also is postulated to be a major factor in the ability of cross-linked PVP to function.[17–19]

In addition to the starches, a large variety of materials have been used and are reported to be effective as disintegrants. This group includes Veegum HV, methylcellulose, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose.[20] Sodium lauryl sulfate in combination with starch also has been demonstrated to be an effective disintegrant. In some cases the apparent effectiveness of surfactants in improving tablet disintegration is postulated as being due to an increase in the rate of wetting.

The disintegrating agent usually is mixed with the active ingredients and diluents prior to granulation. In some cases it may be advantageous to divide the starch into two portions: one part is added to the powdered formula prior to granulation, and the remainder is mixed with the lubricant and added prior to compression. Incorporated in this manner, the starch serves a double purpose; the portion added to the lubricant rapidly breaks down the tablet to granules, and the starch mixed with the active ingredients disintegrates the granules into smaller particles. Veegum has been shown to be more effective as a disintegrator in sulfathiazole tablets when most of the quantity is added after granulation and only a small amount before granulation. Likewise, the montmorillonite clays were found to be good tablet disintegrants when added to prepared granulations as powder. They are much less effective as disintegrants when incorporated within the granules.

Factors other than the presence of disintegrants can affect significantly the disintegration time of compressed tablets. The binder, tablet hardness and the lubricant have been shown to influence the disintegration time. Thus, when the formulator is faced with a problem concerning the disintegration of a compressed tablet, the answer may not lie in the selection and quantity of the disintegrating agent alone.

The evolution of carbon dioxide is also an effective way to cause the disintegration of compressed tablets. Tablets containing a mixture of sodium bicarbonate and an acidulant such as tartaric or citric acid will effervesce when added to water. Sufficient acid is added to produce a neutral or slightly acidic reaction when disintegration in water is rapid and complete. One drawback to the use of the effervescent type of disintegrator is that such tablets must be kept in a dry atmosphere at all times during manufacture, storage and packaging. Soluble, effervescent tablets provide a popular form for dispensing aspirin and noncaloric sweetening agents.

Coloring Agents

Colors in compressed tablets serve functions other than making the dosage form more esthetic in appearance. Color helps the manufacturer to control the product during its preparation, as well as serving as a means of identification to the user. The wide diversity in the use of colors in solid dosage forms makes it possible to use color as an important category in the identification code developed by the AMA to establish the identity of an unknown compressed tablet in situations arising from poisoning.

All colorants used in pharmaceuticals must be approved and certified by the FDA. For several decades colorants have been subjected to rigid toxicity standards and, as a result, a number of colorants have been removed from an approved list of FD&C colors or "delisted." Several have been listed as well. The colorants currently approved in the US are listed in Table 1. Each country has its own list of approved colorants, and formulators must consider this in designing products for the international market.[21]

Any of the approved certified water-soluble FD&C dyes, mixtures of the same or their corresponding lakes may be used to color tablets. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal resulting in an insoluble form of the dye. In some instances multiple dyes are used to give a purposefully heterogeneous coloring in the form of speckling to compressed tablets. The dyes available do not meet all the criteria required for the ideal pharmaceutical colorants. The photosensitivity of several of the commonly used colorants and their lakes has been investigated, as well as the protection afforded by a number of glasses used in packaging tablets.

Another approach for improving the photostability of dyes has been in the use of ultraviolet-absorbing chemicals in the tablet formulations with the dyes. The Di-Pac line (*Amstar*) is a series of commercially available colored, direct-compression sugars.

The most common method of adding color to a tablet formulation is to dissolve the dye in the binding solution prior to the granulating process. Another approach is to adsorb the dye

Table 1—Colors Approved for Use in the US in Oral Dosage Forms[a,b]

Color	Other names	Color Index (CI 1971)	Use restriction (US)
FD & C Red 40	Allura red	16035	FDA certification on each lot of dye
D & C Red 33	Acid fuchsin D	17200	ADI 0–0.76 mg.
	Naphtalone red B		
D & C Red 36			ADI 0—1.0 mg
Canthaxanthinin	Food orange 8	40850	None
D & C Red 22	Eosin Y	45380	FDA certification on each lot of dye
D & C Red 28	Phloxine B	45410	FDA certification on each lot of dye
D & C Red 3	Erythrosine	45430	FDA certification on each lot of dye
Cochineal extract	Natural red 4	75470	None
	Carmine		
Iron oxide—red	—	77491	ADI 0–5 mg elemental iron
FD & C Yellow 6	Sunset yellow FCF	15985	None
	Yellow orange 5		
FD & C Yellow 5	Tartrazine	19140	Label declaration and FDA certification on each lot of dye
D & C Yellow 10	Quinoline yellow WS	47005	FDA certification on each lot of dye
Beta-carotene	—	40800	
Iron oxide—yellow	—	77492	ADI 0–5 mg elemental iron
FD & C Blue 1	Brilliant blue FCF	42090	FDA certification on each lot of dye
FD & C Blue 2	Indigotine	73015	None
	Indigo carmine		
FD & C Green 3	Fast green FCF	42035	FDA certification on each lot of dye
Iron oxide—black	—	77499	ADI 0–5 mg elemental iron
Caramel	Burnt sugar	—	None
Titanium dioxide	—	77891	None

[a] Abbreviations: ADI—Acceptable Daily Intake (per kg body weight)
CI— Color index numbers of 1971 (US)
D & C— Drug and Cosmetic Dyes (US)
FD & C— Food, Drug and Cosmetic Dyes (US)
FDA—Food and Drug Administration (US)

[b] As of February, 1988 and subject to revision.

on starch or calcium sulfate from its aqueous solution; the resultant powder is dried and blended with the other ingredients. If the insoluble lakes are used, they may be blended with the other dry ingredients. Frequently during drying, colors in wet granulations migrate, resulting in an uneven distribution of the color in the granulation. After compression, the tablets will have a mottled appearance due to the uneven distribution of the color. Migration of colors may be reduced by drying the granulation slowly at low temperatures and stirring the granulation while it is drying. The affinity of several water-soluble anionic certified dyes for natural starches has been demonstrated; in these cases this affinity should aid in preventing color migration.

Other additives have been shown to act as dye-migration inhibitors. Tragacanth (1%), acacia (3%), attapulgite (5%) and talc (7%) were effective in inhibiting the migration of FD&C Blue No 1 in lactose. In using dye lakes, the problem of color migration is avoided since the lakes are insoluble. Prevention of mottling can be helped also by the use of lubricants and other additives which have been colored similarly to the granulation prior to their use. The problem of mottling becomes more pronounced as the concentration of the colorants increases. Color mottling is an undesirable characteristic common to many commercial tablets.

Flavoring Agents

In addition to the sweetness which may be afforded by the diluent of the chewable tablet, eg, mannitol or lactose, artificial sweetening agents may be included. Formerly, the cyclamates, either alone or in combination with saccharin, were used widely. With the banning of the cyclamates and the indefinite status of saccharin, new natural sweeteners are being sought. Aspartame (*Searle*), has found applications for pharmaceutical formulations. Sweeteners other than the sugars have the advantage of reducing the bulk volume, considering the quantity of sucrose required to produce the same degree of sweetness. Being present in small quantities, they do not affect markedly the physical characteristics of the tablet granulation.

Powder Compaction

Compressed tablets became a commercially viable and efficient dosage form with the invention of tablet machines. In 1843 William Brockendon, a British inventor, author, artist and watchmaker, received British Patent #9977 for "Shaping Pills, Lozenges, and Black Lead by Pressure in Dies."[22] In over 150 years of tablet manufacture, the basic process has not changed. Surprisingly, improvements have been made only with regards to speed of manufacture and quality control.

The process of compaction has several identifiable phases. As can be seen in Fig 3, when powders undergo compression (a reduction in volume), the first process to occur is a consolidation of the powders. During this consolidation phase, the powder particles adopt a more efficient packing order. The second phase of the compaction process is elastic, or reversible deformation. If the force were to be removed during this phase, the powder would recover completely to the efficiently packed state. For most pharmaceutical powders, this phase is very short in duration, and very difficult to identify on most instrumented tablet presses. The third phase of compaction

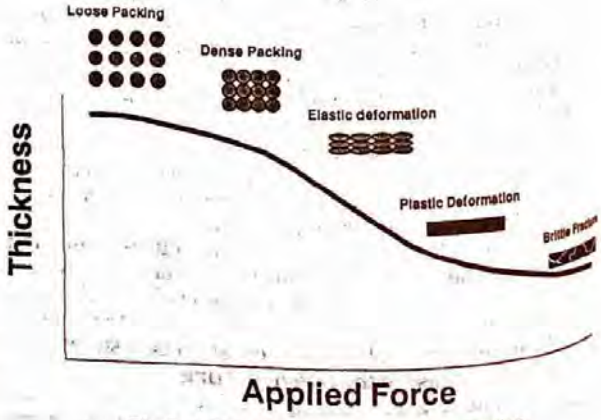


Fig 3. The stages of powder compaction.

is plastic, or irreversible deformation of the powder bed. It is this phase of the compaction process that is the most critical in tablet formation. If too much force is applied to the powder, brittle fracture occurs. If the force was applied to quickly, fracture and debonding during stress relaxation can occur.

In 1950, Stewart reported on the importance of plastic flow, and suggested that if a material has significant plastic flow under compression, it will be more likely to form a compact.[23] David and Augsburger evaluated stress-relaxation data, using the Maxwell model of viscoelastic behavior in an attempt to quantify the rate of plastic deformation of some direct compression excipients.[24] Jones has used the term *contact time* to describe the total time for which a moving punch applies a detectable force to the die contents during the compression and decompression event, excluding ejection.[25]

Rees and Rue evaluated three parameters: stress relation during compaction, effect of contact time on tablet density and rate of application of diametrical compression on tablet deformation.[26]

Jones[25] outlined numerous techniques to evaluate the compactability of powders. Because of the completeness of his review, these parameters are discussed below.

Tablet Strength—Compression Pressure Profile

Most formulators use tablet *hardness*, or tensile strength, as a measure of the cohesiveness of a tablet. With even the simplest of instrumented tablet presses, it is possible to plot tensile strength versus the force applied to the tablet. Figure 4 illustrates such a plot. These plots can be useful in identifying forces which can cause fracture and can lead to a quick, tangible assessment of the compatibility of the formulation. However, there are many limitations to this method, as these plots cannot predict *lamination* or *capping*. In addition, the cohesiveness of a tablet can change upon storage, in either a positive or negative direction.

Tablet Friability

This test is discussed later in the chapter, and there have been many suggestions as to how they should be performed. Many formulators believe this is an important indicator of cohesiveness, but is of limited value in predicting failure in the field.

Changes in Bed Density during Compression

As applied stress (force) increases, elastic and plastic deformation of the particles occurs, which results in plastic flow, and a reduction in inter- and intraparticulate void spaces. This lowers the overall compact density.

For highly cohesive systems, the reduction in void space may yield a compact of sufficient strength for insertion into a capsules shell. However, the inherent cohesiveness for most drugs and excipients is not suitable alone for tablet manufacture.

The Heckel equation is given below; K can be considered to be equal to the reciprocal of the mean yield pressure and A is a function of the original compact volume and is related to the densification and particle rearrangement prior to bonding.

$$\ln\left[\frac{1}{1-D}\right] = KP + A$$

where D is the relative density at pressure P and K and A are constants.

Hersey and Rees[28] have classified Heckel plots into two categories. Figure 5 shows both types of Heckel plots. Type 2 differs from Type 1 in that above a certain pressure a single linear relationship occurs irrespective of the initial bed density. This is independent of particle size and is probable due to fragmentation of particles and their subsequent compaction by plastic deformation. For Type 1 materials, no such fracture occurs, but adjacent particles simply deform plastically.

The pressure at which the plots transition to a linear portion is approximately equal to the minimum pressure required to form a coherent compact.

Changes in Surface Area during Compression

Bulk powders change their state of packing during compaction, and individual particles fracture and/or plastically deform. During this process, the surface area of the powders and the compact in whole, changes. Conventional nitrogen absorption techniques can estimate these changes. Although this can be tedious, these measurements can give a means of examining lamination tendency.

Stress Relaxation

The experimental technique consists of holding the compression process at a point of maximum compression and observing the compression force over various periods of time. By increasing the duration of this period (dwell time), plastic flow is maximized and tablet strength increases.

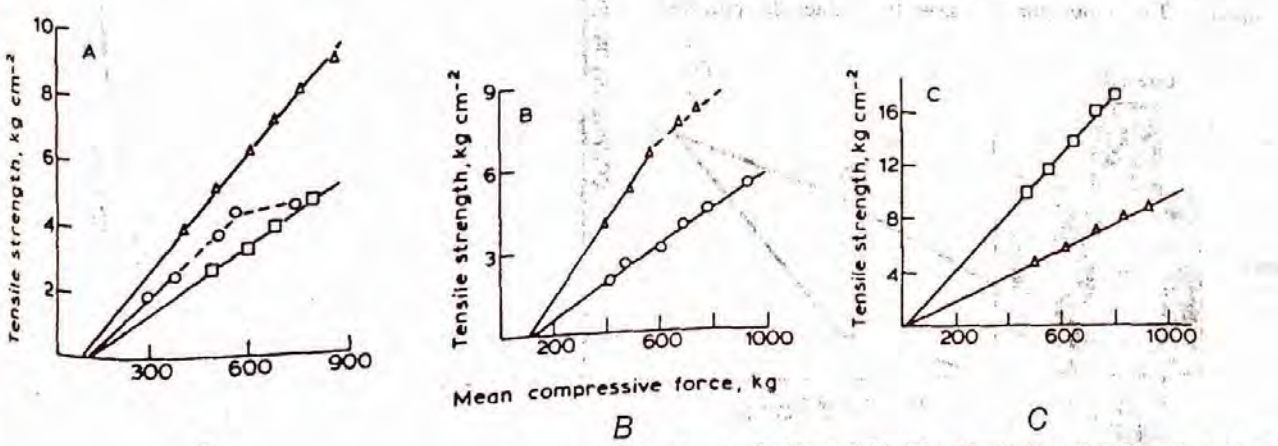
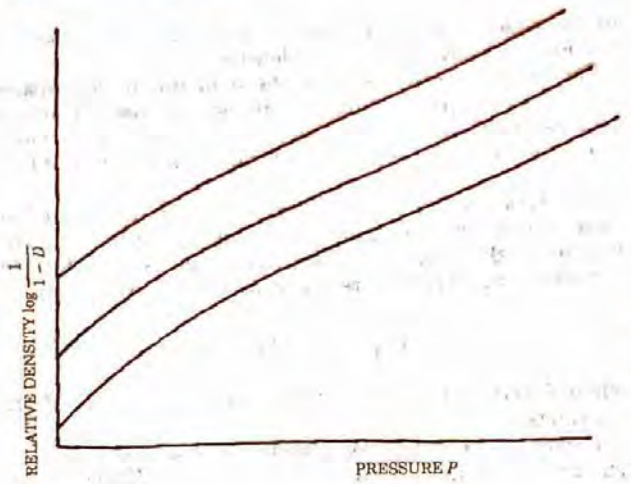


Fig 4. Tensile strength of compacts prepared from different crystal forms. *A:* Barbitone (104–152 μm)—○, Form I; □ Form II; △, Form III. *B:* Sulphathiazole (104–152 μm)—○, Form I; △, Form II. *C:* Aspirin (250–353 μm)—△, Form I; □, Form IV (courtesy, Summers *et al*[27]).



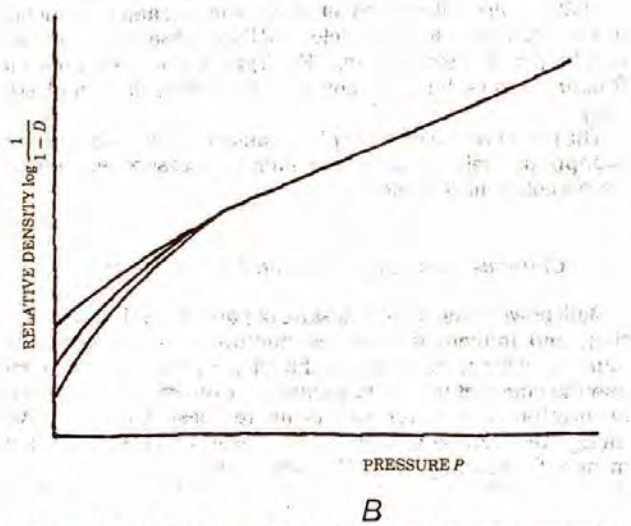


Fig 5. Heckel plots. *A:* Type I; *B:* Type II (courtesy, Jones[29]).

Stress Transmissions during Compression

If the stresses in the upper punch, lower punch and die wall are monitored, as in Fig 6, a general plot can be constructed showing the relationship between these forces. The elastic limit is reached at point *A*. At point *B*, the applied force is released, and the transmitted force on the wall of the die falls rapidly. The upper punch ceases to contact the powder/compact at point *C*, where the transmitted force falls rapidly to a residual force, point *D*. The force needed to eject the tablet from the die must be greater than the residual force holding it to the sides of the die. Therefore, residual forces tend to be proportional to ejection forces. In addition, these plots can give a good assessment of the elastic component of the compaction process of a powder.

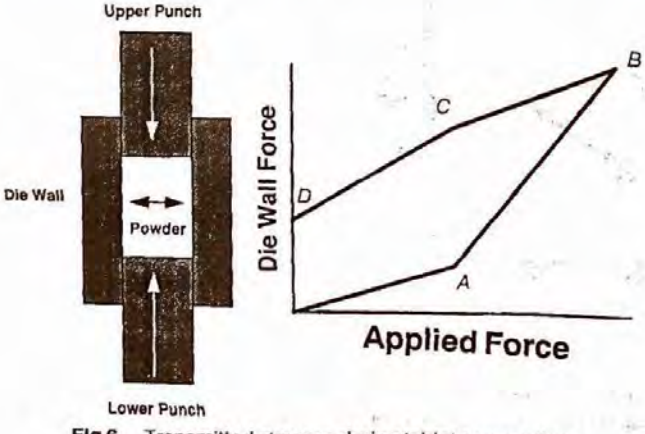
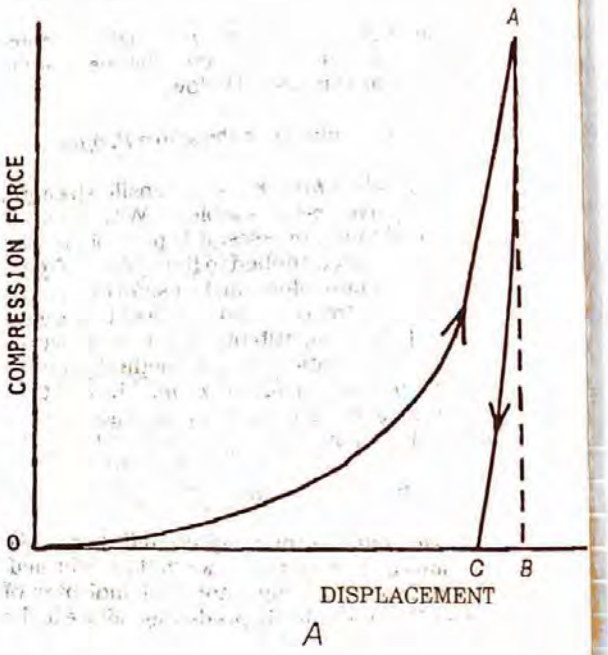


Fig 6. Transmitted stresses during tablet compaction.

Work and Compaction

Force-displacement (*F-D*) curves are useful in determining the "work" involved in forming a compact. Curves, such as shown in Fig 7,[29] represent the work of the compression process, but all compacts expand somewhat during decompression, and this force is transferred back to the punch. Therefore, by performing a second compression of the compact, the second result can be subtracted from the first for a



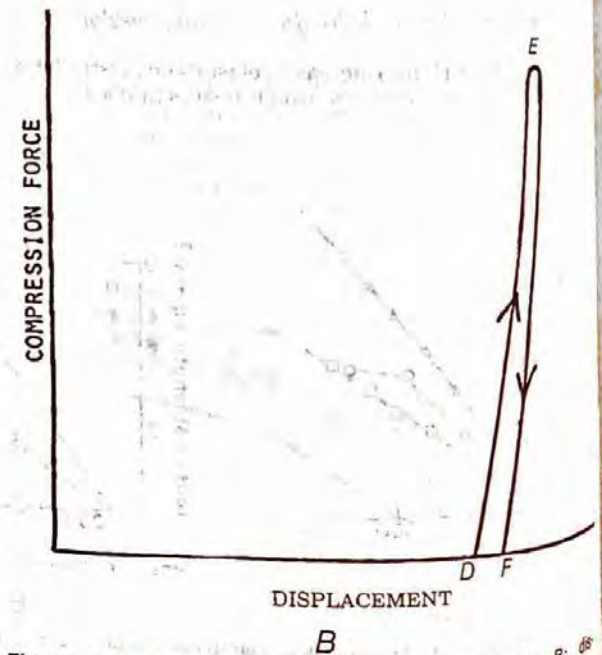


Fig 7. Typical forces. *A:* displacement (*F–D*) curve; *B:* displacement (*F–D*), second compression (courtesy, Jones[29]).

"corrected *F-D* curve." The corrected curve represents the work associated with plastic deformation during powder compaction, as well as a determination of the work of friction of the die wall and the work of elastic deformation.

Granulation Methods

Wet Granulation

The most widely used and most general method of tablet preparation is the wet-granulation method. Its popularity is due to the greater probability that the granulation will meet all the physical requirements for the compression of good tablets. Its chief disadvantages are the number of separate steps involved, as well as the time and labor necessary to carry out the procedure, especially on a large scale. The steps in the wet method are weighing, mixing, granulation, screening the damp mass, drying, dry screening, lubrication and compression. The equipment involved depends on the quantity or size of the batch. The active ingredient, diluent and disintegrant are mixed or blended well. For small batches the ingredients may be mixed in stainless-steel bowls or mortars. Small-scale blending also can be carried out on a large piece of paper by holding the opposite edges and tumbling the material back and forth. The powder blend may be sifted through a screen of suitable fineness to remove or break up lumps. This screening also affords additional mixing. The screen selected always should be of the same type of wire or cloth that will not affect the potency of the ingredients through interaction. For example, the stability of ascorbic acid is affected deleteriously by even small amounts of copper, thus care must be taken to avoid contact with copper or copper-containing alloys.

For larger quantities of powder, the Patterson-Kelley twin-shell blender and the double-cone blender offer a means of precision blending and mixing in short periods of time (Fig 8). Twin-shell blenders are available in many sizes from laboratory models to large production models. Planetary mixers, eg, the Glen mixer and the Hobart mixer, have served this function in the pharmaceutical industry for many years (Fig 9). On a large scale, ribbon blenders also are employed frequently and may be adapted for continuous production procedures. Mass mixers of the sigma-blade type have been used widely in the pharmaceutical industry.

Rapidly increasing in popularity are the high-speed, high-shear mixers such as the Lodige/Littleford, Diosna, Fielder and Baker-Perkins. For these mixers a full range of sizes are available. The processing of granulations in these machines is generally faster than in conventional granulators. However, control over the process is critical, and scale-up issues may become extremely important.[30] Fluid-bed granulation (discussed below) also is gaining wide acceptance in the industry. For both of these types of processing, slight modifications to the following procedures are required.

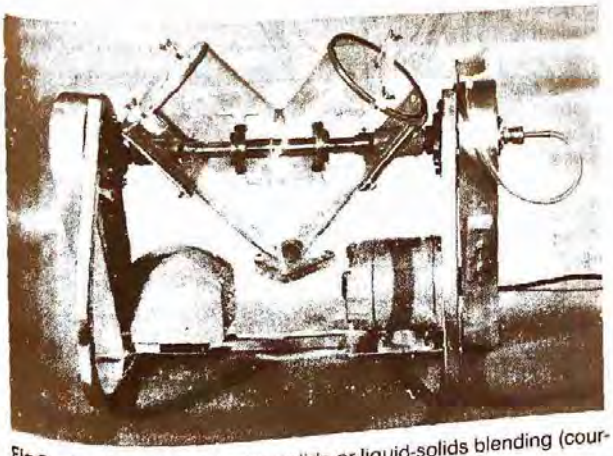


Fig 8. Twin-shell blender for solids or liquid-solids blending (courtesy, Patterson-Kelley).

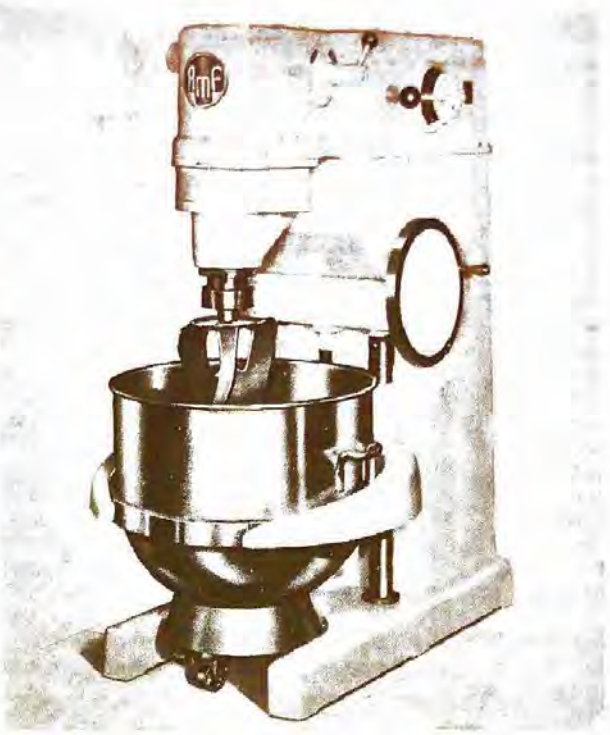


Fig 9. The Glen powder mixer (courtesy, Am Machine).

Solutions of the binding agent are added to the mixed powders with stirring. The powder mass is wetted with the binding solution until the mass has the consistency of damp snow or brown sugar. If the granulation is overwetted, the granules will be hard, requiring considerable pressure to form the tablets, and the resultant tablets may have a mottled appearance. If the powder mixture is not wetted sufficiently, the resulting granules will be too soft, breaking down during lubrication and causing difficulty during compression.

The wet granulation is forced through a 6- or 8-mesh screen. Small batches can be forced through by hand using a manual screen. For larger quantities, one of several comminuting mills suitable for wet screening can be used. These include the Stokes oscillator, Colton rotary granulator, Fitzpatrick comminuting mill or Stokes tornado mill. See Fig 10. In comminuting mills the granulation is forced through the sieving device by rotating hammers, knives or oscillating bars. Most high-speed mixers are equipped with a chopper blade which operates independently of the main mixing blades and can replace the wet milling step, ie, can obviate the need for a separate operation.

For tablet formulations where continuous production is justified, extruders such as the Reitz extructor have been adapted for the wet-granulation process. The extruder consists of a screw mixer with a chamber where the powder is mixed with the binding agent and the wet mass gradually is forced through a perforated screen forming threads of the wet granulation. The granulation then is dried by conventional methods. A semiautomatic continuous process using the Reitz extructor has been described for the preparation of the antacid tablet Gelusil (*Warner-Lambert*).

Moist material from the wet milling step is placed on large sheets of paper on shallow wire trays and placed in drying cabinets with a circulating air current and thermostatic heat control. See Fig 11. While tray drying was the most widely used method of drying tablet granulations in the past, fluid-bed drying is now equally popular. Notable among the newer methods being introduced are the fluid-bed dryers. In drying

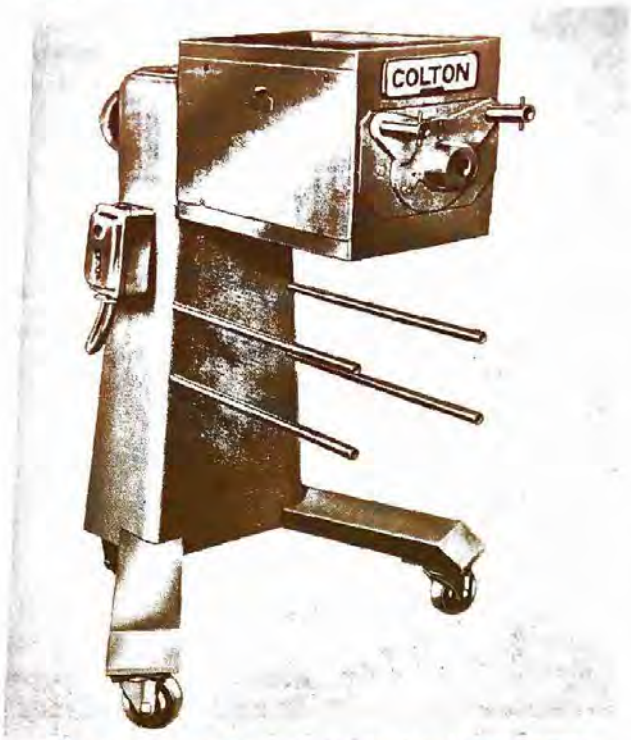


Fig 10. Rotary granulator and sifter (courtesy, Vector/Colton).

tablet granulation by fluidization, the material is suspended and agitated in a warm air stream while the granulation is maintained in motion. Drying tests comparing the fluidized bed and a tray dryer for a number of tablet granulations indicated that the former was 15 times faster than the conventional method of tray drying. In addition to the decreased drying time, the fluidization method is claimed to have other advantages such as better control of drying temperatures, decreased handling costs and the opportunity to blend lubricants and other materials into the dry granulation directly in the fluidized bed. See Fig 12.[31]

The application of radio-frequency drying and infrared drying to tablet granulations has been reported as successful for the majority of granulations tried. These methods readily lend themselves to continuous granulation operations. The study of drying methods for tablet granulations led to the development of the Rovac dryer system by Ciba pharmacists and engineers. The dryer is similar in appearance to the cone blender except for the heating jacket and vacuum connections. By excluding oxygen and using the lower drying temperatures made possible by drying in a vacuum, opportunities for degradation of the ingredients during the drying cycle are minimized. A greater uniformity of residual moisture content is achieved because of the moving bed, controlled temperature and controlled time period of the drying

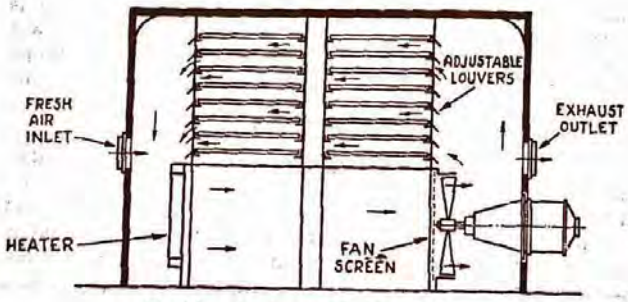


Fig 11. Cross section of tray dryer.

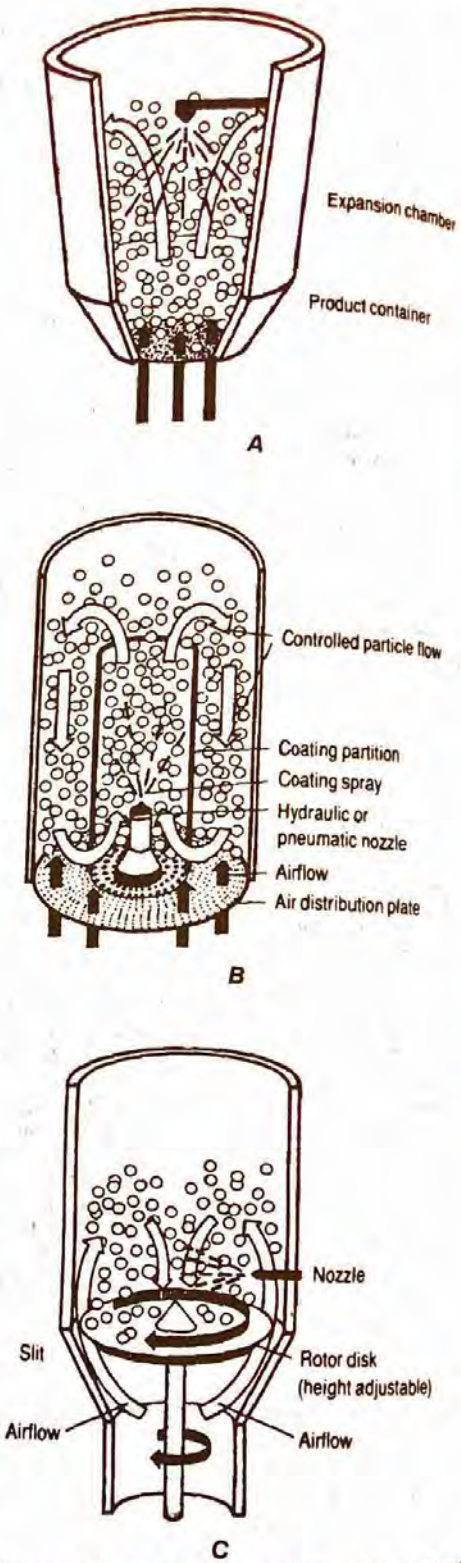


Fig 12. Three versions of fluidized-bed granulation and drying. *A:* Top-spray method used in conventional fluid-bed granulation coaters; *B:* bottom-spray method used in Wurster air-suspension columns; *C:* tangential-spray method used in rotary fluid-bed coaters/granulators (courtesy, Aster Publ, adapted from Ref 31).

cycle. Particle-size distribution can be controlled by varying the speed of rotation and drying temperature as well as by comminuting the granulation to the desired granule size after drying.

In drying granulations it is desirable to maintain a residual amount of moisture in the granulation. This is necessary to maintain the various granulation ingredients such as gums in a hydrated state. Also, the residual moisture contributes to the reduction of the static electric charges on the particles. In the selection of any drying process, an effort is made to obtain a uniform moisture content. In addition to the importance of moisture content of the granulation in its handling during the manufacturing steps, the stability of the products containing moisture-sensitive active ingredients may be related to the moisture content of the products.

Previously it was indicated that water-soluble colorants can migrate toward the surface of the granulation during the drying process, resulting in mottled tablets after compression. This is also true for water-soluble drug substances, resulting in tablets unsatisfactory as to content uniformity. Migration can be reduced by drying the granulation slowly at low temperatures or using a granulation in which the major diluent is present as granules of large particle size. The presence of microcrystalline cellulose in wet granulations also reduces migration tendencies.

After drying, the granulation is reduced in particle size by passing it through a smaller mesh screen. Following dry screening, the granule size tends to be more uniform. For dry granulations the screen size to be selected depends on the diameter of the punch. The following sizes are suggested:

Tablets up to 3/16 inch diam, use 20-mesh
Tablets 7/32 in to 5/16 inch, use 16-mesh
Tablets 11/32 in to 13/32 inch, use 14-mesh
Tablets 7/16 inch and larger, use 12-mesh

For small amounts of granulation, hand screens may be used and the material passed through with the aid of a stainless-steel spatula. With larger quantities, any of the comminuting mills with screens corresponding to those just mentioned may be used. Note that the smaller the tablet, the finer the dry granulation to enable more uniform filling of the die cavity; large granules give an irregular fill to a comparatively small die cavity. With compressed tablets of sodium bicarbonate, lactose and magnesium trisilicate, a relationship has been demonstrated to exist between the particle size of the granulated material and the disintegration time and capping of the resultant tablets. For a sulfathiazole granulation, however, the particle-size distribution did not appear to influence hardness or disintegration.

After dry granulation, the lubricant is added as a fine powder. It usually is screened onto the granulation through 60- or 100-mesh nylon cloth to eliminate small lumps as well as to increase the covering power of the lubricant. As it is desirable for each granule to be covered with the lubricant, the lubricant is blended with the granulation very gently, preferably in a blender using a tumbling action. Gentle action is desired to maintain the uniform granule size resulting from the granulation step. It has been claimed that too much fine powder is not desirable because fine powder may not feed into the die evenly; consequently, variations in weight and density result. Fine powders, commonly designated as *fines*, also blow out around the upper punch and down past the lower punch, making it necessary to clean the machine frequently. Fines, however, at a level of 10 to 20% traditionally are sought by the tablet formulator. The presence of some fines is necessary for the proper filling of the die cavity. Now, even higher concentrations of fines are used successfully in tablet manufacture. Most investigators agree that no general limits exist for the amount of fines that can be present in a granulation but must be determined for each specific formula.

Many formulators once believed (and some still believe) that overblending resulted in an increased amount of fines and, hence, caused air entrapment in the formula. The capping and laminating of tablets associated with overblending lubricants was thought to be caused by these air pockets. Most scientists now recognize that a more plausible explanation has to do with the function of the lubricants themselves. Since the very nature of lubricant tends to make surfaces less susceptible to adhesion, overblending prevents the intergranule bonding that takes place during compaction.

Fluid-Bed Granulation

A new method for granulating evolved from the fluid-bed drying technology described earlier. The concept was to spray a granulating solution onto the suspended particles which then would be dried rapidly in the suspending air. The main benefit from this system is the rapid granulation and drying of a batch. The two main firms that developed this technology are *Glatt* and *Aeromatic*. The design of these systems are basically the same with both companies (see Fig 12). In this method, particles of an inert material, or the active drug, are suspended in a vertical column with a rising air stream; while the particles are suspended, the common granulating materials in solution are sprayed into the column. There is a gradual particle buildup under a controlled set of conditions resulting in a tablet granulation which is ready for compression after the addition of the lubricant. An obvious advantage exists since granulating and drying can take place in a single piece of equipment. It should be noted, however, that many of the mixers discussed previously can be supplied with a steam jacket and vacuum, and can provide the same advantage.

In these systems a granulating solution or solvent is sprayed into or onto the bed of suspended particles. The rate of addition of the binder, temperature in the bed of particles, temperature of the air, volume and moisture of the air all play an important role in the quality and performance of the final product. Many scientists feel that this method is an extension of the wet-granulation method, as it incorporates many of its concepts. However anyone who has developed a formulation in a fluid-bed system knows that the many operating parameters involved make it somewhat more complex.[31] In addition to its use for the preparation of tablet granulations this technique also has been proposed for the coating of solid particles as a means of improving the flow properties of small particles. Researchers have observed that, in general, fluid-bed granulation yields a less dense particle than conventional methods, and this can affect subsequent compression behavior. A large-scale fluid-bed granulation process has been described for Tylenol (*McNeil*). Methods for the preparation of compressed tablets have been reviewed in the literature.[32]

In the *Merck Sharp & Dohme* facility at Elkton, VA, the entire tablet manufacturing process based on a wet-granulation method is computer-controlled. By means of a computer, the system weighs the ingredients, blends, granulates, dries and lubricates to prepare a uniform granulation of specified particle size and particle-size distribution. The computer directs the compression of the material into tablets having exacting specifications for thickness, weight and hardness. After compression, the tablets are coated with a water-based film coating. The computer controls and monitors all flow of material. The plant represents the first totally automated pharmaceutical manufacturing facility. See Fig 13.

Although the Merck facility represents the most fully automated production operation, there are many others throughout the industry which have parts of the operation (such as a coating, compressing or fluid-bed granulation process) operating under a high degree of sophistication and automation. This is the trend for the future. Equipment suppliers work closely with individual pharmaceutical companies in designing specialized and unique systems.

Dry Granulation

When tablet ingredients are sensitive to moisture or are unable to withstand elevated temperatures during drying, and when the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form granules. This method is referred to as dry granulation, precompression

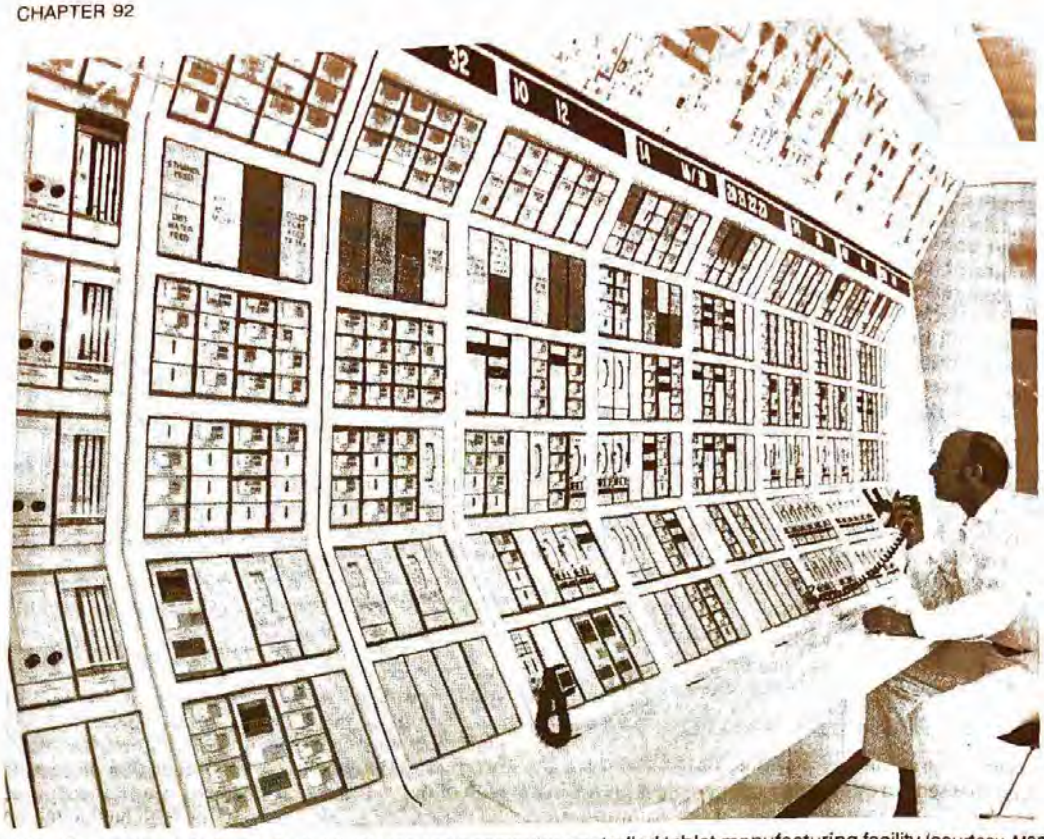


Fig 13. Computer control room for the first large-scale computer-controlled tablet manufacturing facility (courtesy, MSD).

or double-compression. It eliminates a number of steps but still includes weighing, mixing, slugging, dry screening, lubrication and compression. The active ingredient, diluent (if one is required) and part of the lubricant are blended. One of the constituents, either the active ingredient or the diluent, must have cohesive properties. Powdered material contains a considerable amount of air; under pressure this air is expelled and a fairly dense piece is formed. The more time allowed for this air to escape, the better the tablet or slug.

When slugging is used, large tablets are made as slugs because fine powders flow better into large cavities. Also, producing large slugs decreases production time; ⅞ to 1 in are the most practical sizes for slugs. Sometimes, to obtain the pressure which is desired the slug sizes are reduced to ¾ in. The punches should be flat-faced. The compressed slugs are comminuted through the desirable mesh screen either by hand, or for larger quantities through the Fitzpatrick or similar comminuting mill. The lubricant remaining is added to the granulation, blended gently and the material is compressed into tablets. Aspirin is a good example where slugging is satisfactory. Other materials such as aspirin combinations, acetophenetidin, thiamine hydrochloride, ascorbic acid, magnesium hydroxide and other antacid compounds may be treated similarly.

Results comparable to those accomplished by the slugging process also are obtained with compacting mills. In the compaction method the powder to be densified passes between high-pressure rollers which compress the powder and remove the air. The densified material is reduced to a uniform granule size and compressed into tablets after the addition of a lubricant. Excessive pressures which may be required to obtain cohesion of certain materials may result in a prolonged dissolution rate. Compaction mills available include the Chilsonator (*Fitzpatrick*), Roller Compactor (*Vector*) and the Compactor Mill (*Allis-Chalmers*).

Direct Compression

As its name implies, direct compression consists of compressing tablets directly from powdered material without modifying the physical nature of the material itself. Formerly direct compression as a method of tablet manufacture was reserved for a small group of crystalline chemicals having all the physical characteristics required for the formation of a good tablet. This group includes chemicals such as potassium salts (chlorate, chloride, bromide, iodide, nitrate, permanganate), ammonium chloride and methenamine. These materials possess cohesive and flow properties which make direct compression possible.

Since the pharmaceutical industry constantly is making efforts to increase the efficiency of tableting operations and reduce costs by using the smallest amount of floor space and labor as possible for a given operation, increasing attention is being given to this method of tablet preparation. Approaches being used to make this method more universally applicable include the introduction of formulation additives capable of imparting the characteristics required for compression, and the use of force-feeding devices to improve the flow of powder blends.

For tablets in which the drug itself constitutes a major portion of the total tablet weight, it is necessary that the drug possess those physical characteristics required for the formulation to be compressed directly. Direct compression for tablets containing 25% or less of drug substances frequently can be used by formulating with a suitable diluent which acts as a carrier or vehicle for the drug.[32–34]

Direct-compression vehicles or carriers must have good flow and compressible characteristics. These properties are imparted to them by a preprocessing step such as wet granulation, slugging, spray drying, spheronization or crystallization. These vehicles include processed forms of most of the common diluents including dicalcium phosphate dihydrate, trical-

cium phosphate, calcium sulfate, anhydrous lactose, spray-dried lactose, pregelatinized starch, compressible sugar, mannitol and microcrystalline cellulose. These commercially available direct-compression vehicles may contain small quantities of other ingredients (eg, starch) as processing aids.

Dicalcium phosphate dihydrate (Di-Tab, *Stauffer*) in its unmilled form has good flow properties and compressibility. It is a white crystalline agglomerate insoluble in water and alcohol. The chemical is odorless, tasteless and nonhygroscopic. Since it has no inherent lubricating or disintegrating properties, other additives must be present to prepare a satisfactory formulation.

Compressible sugar consists mainly of sucrose that is processed to have properties suitable for direct compression. It also may contain small quantities of dextrin, starch or invert sugar. It is a white crystalline powder with a sweet taste and complete water solubility. It requires the incorporation of a suitable lubricant at normal levels for lubricity. The sugar is used widely for chewable vitamin tablets because of its natural sweetness. One commercial source is Di-Pac (*Amstar*) prepared by the cocrystallization of 97% sucrose and 3% dextrins. Some forms of lactose meet the requirements for a direct-compression vehicle. Hydrous lactose does not flow and its use is limited to tablet formulations prepared by the wet granulation method. Both anhydrous lactose and spray-dried lactose have good flowability and compressibility and can be used in direct compression provided a suitable disintegrant and lubricant are present. Mannitol is a popular diluent for chewable tablets due to its pleasant taste and mouth-feel resulting from its negative heat of solution. In its granular form (*ICI Americas*) it has good flow and compressible qualities. It has a low moisture content and is not hygroscopic.

The excipient that has been studied extensively as a direct compression vehicle is microcrystalline cellulose (Avicel, *FMC*). This nonfibrous form of cellulose is obtained by spray-drying washed, acid-treated cellulose and is available in several grades which range in average particle size from 20 to 100 μm. It is water insoluble but the material has the ability to draw fluid into a tablet by capillary action; it swells on contact and thus acts as a disintegrating agent. The material flows well and has a degree of self-lubricating qualities, thus requiring a lower level of lubricant as compared to other excipients.

Forced-flow feeders are mechanical devices available from pharmaceutical equipment manufacturers designed to deaerate light and bulky material. Mechanically, they maintain a steady flow of powder moving into the die cavities under moderate pressure. By increasing the density of the powder, higher uniformity in tablet weights is obtained. See Fig 14.

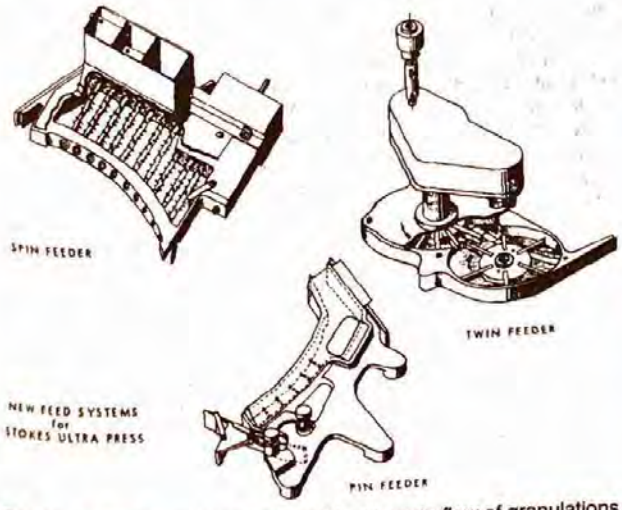


Fig 14. Feeding devices designed to promote flow of granulations for high-speed machines (courtesy, Stokes/Pennwalt).

Recently, many companies have reversed their optimism for some direct-compression systems. Some formulations made by direct compression were not as "forgiving" as were the older wet-granulated products. As raw material variations occurred, especially with the drug, many companies found themselves with poorly compactable formulations. Interest in direct compression also is stimulating basic research on the flowability of powders with and without the presence of additives. Direct compression formulas are included in the formula section found on page 1636.

Related Granulation Processes

Spheronization—Spheronization, a form of pelletization, refers to the formation of spherical particles from wet granulations. Since the particles are round, they have good flow properties when dried. They can be formulated to contain sufficient binder to impart cohesiveness for tableting. Spheronization equipment such as the Marumerizer (*Luwa*) and the CF-Granulator (*Vector*) is commercially available. A wet granulation containing the drug substance, diluent (if required) and binder, is passed first through an extruding machine to form rod-shaped cylindrical segments ranging in diameter from 0.5 to 12 mm. The segment diameter and the size of the final spherical particle depend on the extruder screen size. After extrusion the segments are placed into the Marumerizer where they are shaped into spheres by centrifugal and frictional forces on a rotating plate (see Fig 15). The pellets then are dried by conventional methods, mixed with suitable lubricants and compressed into tablets, or used as capsule-fill material. Microcrystalline cellulose has been shown to be an effective diluent and binder in granulations to be spheronized.[35–38] The advantages of the process include the production of granules, regular in shape, size and surface characteristics; low friability resulting in fewer fines and dust; and the ability to regulate the size of the spheres within a narrow particle-size distribution.

Spheres also can be produced by fluid-bed granulation techniques and by other specialized equipment such as the CF-Granulator (*Vector*). These processes, however, must begin with crystals or nonpareil seeds followed by buildup. Exact results, such as sphere density, are different for the various methods and could be important in product performance. These processes can be run as batches or continuously.

Spray-Drying—A number of tableting additives suitable for direct compression have been prepared by the drying process known as spray-drying. The method consists of bringing together a highly dispersed liquid and a sufficient volume of hot air to produce evaporation and drying of the liquid droplets. The feed liquid may be a solution, slurry, emulsion, gel or paste, provided it is pumpable and capable of being atomized. As shown in Fig 16, the feed is sprayed into a current of warm filtered air. The air supplies the heat for

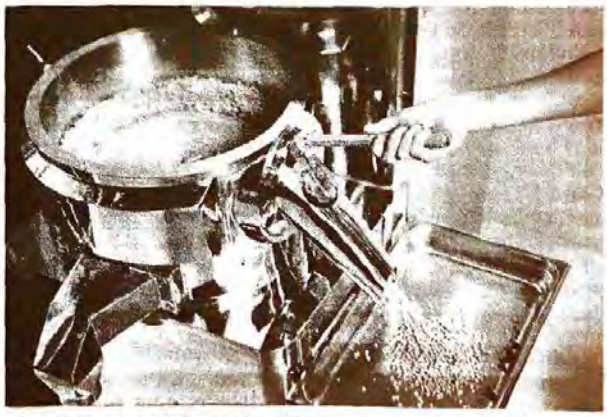


Fig 15. The inside of a QJ-400 Marumerizer (courtesy, Luwa).

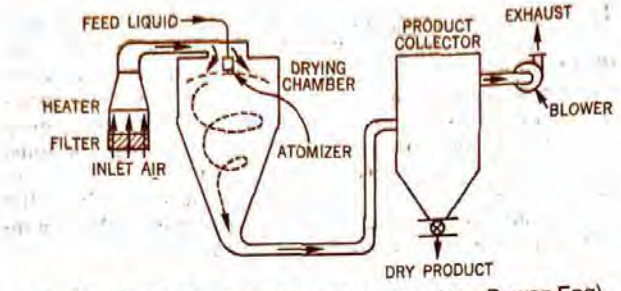


Fig 16. Typical spray-drying system (courtesy, Bowen Eng).

evaporation and conveys the dried product to the collector; the air is then exhausted with the moisture. As the liquid droplets present a large surface area to the warm air, local heat and transfer coefficients are high.

The spray-dried powder particles are homogeneous, approximately spherical in shape, nearly uniform in size and frequently hollow. The latter characteristic results in low bulk density with a rapid rate of solution. Being uniform in size and spherical, the particles possess good flowability. The design and operation of the spray-dryer can vary many characteristics of the final product, such as particle size and size distribution, bulk and particle densities, porosity, moisture content, flowability and friability. Among the spray-dried materials available for direct compression formulas are lactose, mannitol and flour. Another application of the process in tableting is spray-drying the combination of tablet additives as the diluent, disintegrant and binder. The spray-dried material then is blended with the active ingredient or drug, lubricated and compressed directly into tablets.

Since atomization of the feed results in a high surface area, the moisture evaporates rapidly. The evaporation keeps the product cool and as a result the method is applicable for drying heat-sensitive materials. Among heat-sensitive pharmaceuticals successfully spray-dried are the amino acids; antibiotics as aureomycin, bacitracin, penicillin and streptomycin; ascorbic acid; cascara extracts; liver extracts; pepsin and similar enzymes; protein hydrolysates and thiamine.[39]

Frequently, spray-drying is more economical than other processes since it produces a dry powder directly from a liquid and eliminates other processing steps as crystallization, precipitation, filtering or drying, particle-size reduction and particle classifying. By the elimination of these steps, labor, equipment costs, space requirements and possible contamination of the product are reduced. Intrinsic factor concentrate obtained from hog mucosa previously was prepared by *Lederle* using a salt-precipitation process, followed by a freeze-drying. By using spray-drying it was possible to manufacture a high-grade material by a continuous process. The spherical particles of the product facilitated its subsequent blending with vitamin B_{12}. Similar efficiencies have been found in processes producing magnesium trisilicate and dihydroxyaluminum sodium carbonate; both chemicals are used widely in antacid preparations.

Encapsulation of chemicals also can be achieved using spray-drying equipment. The process is useful in coating one material on another in order to protect the interior substance or to control the rate of its release. The substance to be coated can either be liquid or solid, but must be insoluble in a solution of the coating material. The oil-soluble vitamins, A and D, can be coated with a variety of materials such as acacia gum to prevent their deterioration. Flavoring oils and synthetic flavors are coated to give the so-called dry flavors.

Spray-Congealing—Also called spray-chilling, spray-congealing is a technique similar to spray-drying. It consists of melting solids and reducing them to beads or powder by spraying the molten feed into a stream of air or other gas. The same basic equipment is used as with spray-drying although no source of heat is required. Either ambient or cooled air is used depending on the freezing point of the product. For example, monoglycerides and similar materials are spray-congealed with air at 50°F. A closed-loop system with refrigeration cools and recycles the air. Using this process, drugs can be dissolved or suspended in a molten wax and spray-congealed; the resultant material then can be adapted for a prolonged-release form of the drug.

Among the carbohydrates used in compressed tablets, mannitol is the only one which possesses high heat stability. Mannitol melts at 167° and, either alone or in combination with other carbohydrates, can be fused and spray-congealed. Selected drugs have been shown to be soluble in these fused mixtures, and the resultant spray-congealed material possesses excellent flow and compression characteristics.

Tablet Machines

As mentioned previously, the basic mechanical unit in tablet compression involves the operation of two steel punches within a steel die cavity. The tablet is formed by the pressure exerted on the granulation by the punches within the die cavity or cell. The tablet assumes the size and shape of the punches and die used. See Figs 17 and 18. While round tablets are used more generally, shapes such as oval, capsule-form, square, triangular or other irregular shapes may be used. Likewise, the curvature of the faces of the punches determines the curvature of the tablets. The diameters generally found to be satisfactory and frequently referred to as standard are as follows: 3/16, 7/32, 1/4, 9/32, 5/16, 11/32, 7/16, 1/2, 9/16, 5/8, 11/16 and 3/4 inch. Punch faces with ridges are used for compressed tablets scored for breaking into halves or fourths, although it has been indicated that variation among tablet halves is significantly greater than among intact tablets. However, a patented formulation[40] for a tablet scored to form a groove which is one-third to two-thirds the depth of the total tablet thickness is claimed to give equal parts containing substantially equal amounts of the drug substance. Tablets, engraved or embossed with symbols or initials, require punches with faces embossed or engraved with the corresponding designs. See Figs 19 and 20. The use of the tablet sometimes determines its shape; effervescent tablets are usually large, round and flat, while vitamin tablets frequently are prepared in capsule-shaped forms. Tablets prepared using deep-cup punches appear to be round and when coated take on the appearance of pills. Veterinary tablets often have a bolus shape and are much larger than those used in medical practice.

The quality-control program for punches and dies, frequently referred to as tooling, instituted by large pharmaceutical companies emphasizes the importance of their care in modern pharmaceutical production. To produce physically perfect compressed tablets, an efficient punch-and-die program must be set up. Provisions for inspection of tooling, parameters for cost-per-product determination, product identification and tooling specifications must all be considered. A committee of the Industrial and Pharmaceutical Technology Section of the APhA Academy of Pharmaceutical Sciences has established a set of dimensional specifications and tolerances for standard punches and dies.[41]

Regardless of the size of the tableting operation, the attention which must be given to the proper care of punches and dies should be noted. They must be highly polished and kept free from rust and imperfections. In cases where the material pits or abrades the dies, chromium-plated dies have been used. Dropping the punches on hard surfaces will chip their fine edges. When the punches are in the machine, the upper and lower punches should not be allowed to contact each

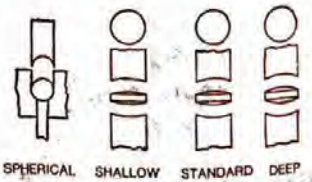


Fig 17. Concave punches.

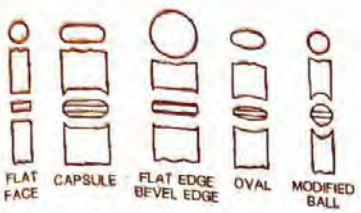


Fig 18. Specially shaped punches.

other. Otherwise, a curling or flattening of the edges will result which is one of the causes of capping. This is especially necessary to observe in the case of deep-cup punches.

When the punches are removed from the machine, they should be washed thoroughly in warm soapy water and dried well with a clean cloth. A coating of grease or oil should be rubbed over all parts of the dies and punches to protect them from the atmosphere. They should be stored carefully in boxes or paper tubes.

Single-Punch Machines

The simplest tableting machines available are those having the single-punch design. A number of models are available as outlined in Table 2. While the majority of these are power-driven, several hand-operated models are available. Compression is accomplished on a single-punch machine as shown in Fig 21. The feed shoe filled with the granulation is positioned over the die cavity which then fills. The feed shoe retracts and scrapes all excess granulation away from the die cavity. The upper punch lowers to compress the granulation within the die cavity. The upper punch retracts and the lower punch rises to eject the tablet. As the feed shoe returns to fill the die cavity, it pushes the compressed tablet from the die platform. The weight of the tablet is determined by the volume of the die cavity; the lower punch is adjustable to increase or decrease the volume of granulation, thus increasing or decreasing the weight of the tablet.

For tablets having diameters larger than ½ inch, sturdier models are required. This is also true for tablets requiring a high degree of hardness as in the case of compressed lozenges.

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

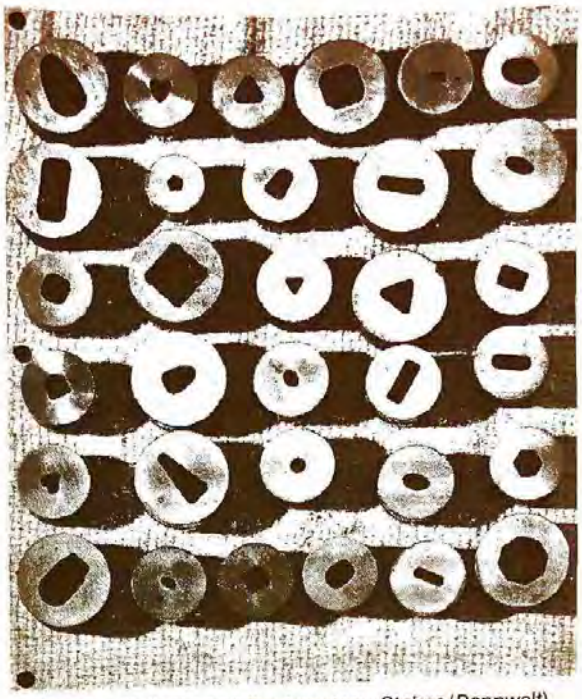


Fig 20. Collection of dies (courtesy, Stokes/Pennwalt).

The heavier models are capable of much higher pressures and are suitable for slugging.

Operation of Single-Punch Machines

In installing punches and dies in a single-punch machine insert the lower punch first by lining up the notched groove on the punch with the lower punch setscrew and slipping it into the smaller bore in the die table; the setscrew is not tightened as yet. The lower punch is differentiated from the upper punch in that it has a collar around the punch head. Slip the die over the punch head so that the notched groove (with the widest area at the top) lines up with the die setscrew. Tighten the lower punch setscrew after seating the lower punch by pressing on the punch with the thumb. Tighten the die setscrew, making certain that the surface of the die is flush with the die table. Insert the upper punch, again lining up the grooved notch with the upper punch setscrew. To be certain that the upper punch is seated securely, turn the machine over by hand with a block of soft wood or wad of cloth between the upper and lower punches. When the punch is seated, tighten the upper punch setscrew. Adjust the pressure so that the upper and lower punches will not come in contact with each other when the machine is turned over. Adjust the lower punch so that it is flush with the die table at the ejection point. Install the feed shoe and hopper.

After adding a small amount of granulation to the hopper, turn the machine over by hand and adjust the pressure until a tablet is formed. Adjust the tablet weight until the desired weight is obtained. The pressure will have to be altered concurrently with the weight adjustments. It should be remembered that as the fill is increased the lower punch moves further away from the upper punch and more pressure will have to be applied to obtain comparable hardness. Conversely, when the fill is decreased, the pressure will have to be decreased. When all the adjust-

Table 2—Single-Punch Tablet Machines

Machine model	Maximum tablet diameter (inches)	Press speed (tablets/min)	Depth of fill (inches)
Stokes-Pennwalt equipment[a]			
511-5	½	40–75	7/16
206-4	1¾	10–40	1 1/16
530-1	2	12–48	1⅝
525-2	3	16–48	2
Manesty equipment (Thomas Eng)			
Hand machine	½	100	7/16
Model F3	⅞	85	1 1/16
Model 35T[a]	3	36	2¼

[a] Widely used for veterinary boluses.

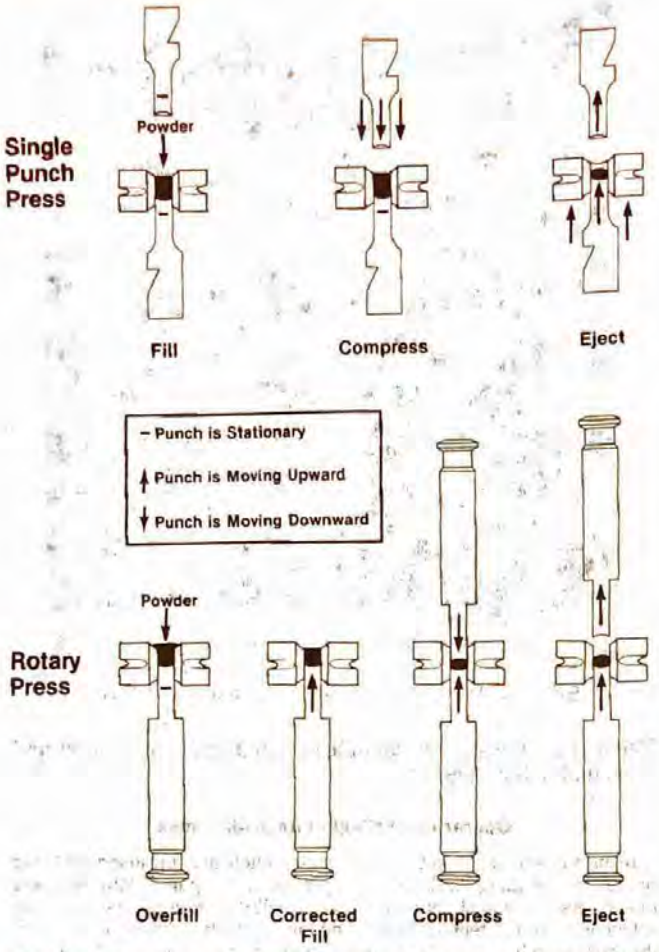


Fig 21. The steps associated with single-punch and rotary tablet machines.

ments have been made, fill the hopper with granulation and turn on the motor. Hardness and weight should be checked immediately and suitable adjustments made if necessary. Periodic checks should be made on the tablet hardness and weight during the running of the batch at 15- to 30-minute intervals.

When the batch has been run off, turn off the power and remove loose dust and granulation with the vacuum cleaner. Release the pressure from the punches. Remove the feed hopper and the feed shoe. Remove the upper punch, the lower punch and the die. Clean all surfaces of the tablet machine and dry well with clean cloth. Cover surfaces with thin coating of grease or oil prior to storage.

As tablets are ejected from the machine after compression, they usually are accompanied with powder and uncompressed granulation. To remove this loose dust, the tablets are passed over a screen, which may be vibrating, and cleaned with a vacuum line.

Rotary Tablet Machines

For increased production, rotary machines offer great advantages. A head carrying a number of sets of punches and dies revolves continuously while the tablet granulation runs from the hopper, through a feed frame and into the dies placed in a large, steel plate revolving under it. This method promotes a uniform fill of the die and therefore an accurate weight for the tablet. Compression takes place as the upper and lower punches pass between a pair of rollers as can be seen in Fig 21. This action produces a slow squeezing effect on the material in the die cavity from the top and bottom and so gives a chance for the entrapped air to escape. The lower punch lifts up and ejects the tablet. Adjustments for tablet weight and hardness can be made without the use of tools

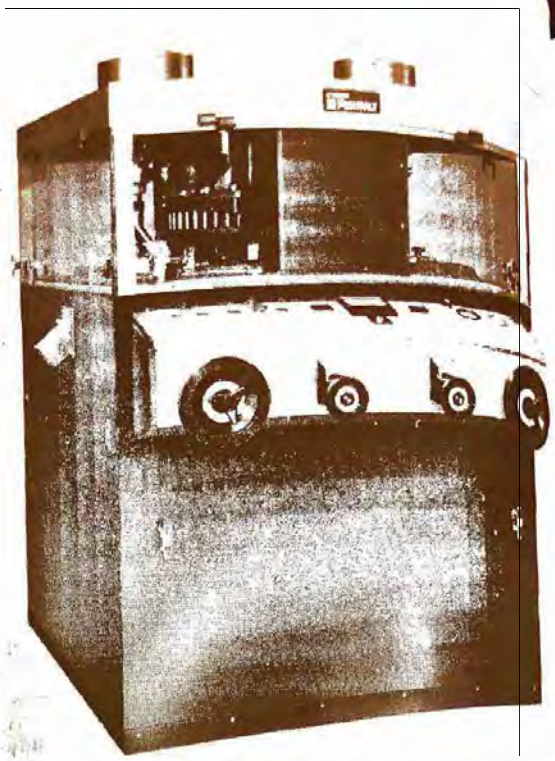


Fig 22. Model 747 High Speed Press, double-sided rotary compacting press designed to produce at speeds over 10,000/min (courtesy Stokes/Pennwalt).

while the machine is in operation. Figure 23 shows the tooling in a 16-station rotary press in the positions of a complete cycle to produce 1 tablet per set of tooling. One of the factors which contributes to the variation in tablet weight and hardness during compression is the internal flow of the granulation within the feed hopper.

On most rotary machine models there is an excess pressure release which cushions each compression and relieves the machine of all shocks and undue strain. The punches and dies can be removed readily for inspection, cleaning and inserting different sets to produce a great variety of sizes and shapes. Many older presses have been modernized with protective shields to prevent physical injury and to comply with OSHA standards (see Fig 24). It is possible to equip the machine with as few punches and dies as the job requires and thus economize on installation costs. For types of rotary machines available, see Table 3.

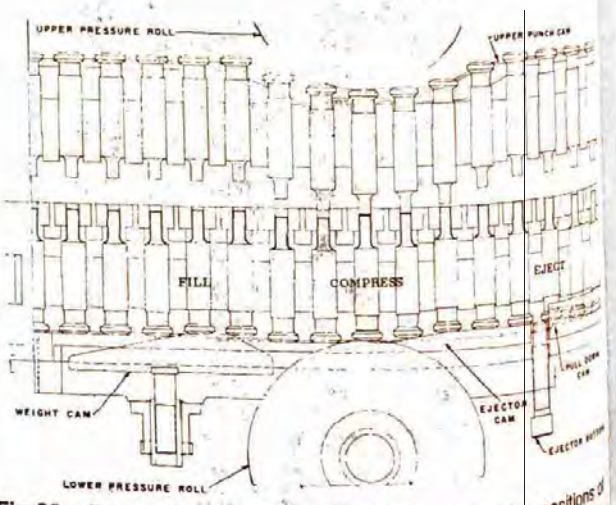


Fig 23. Tooling for a 16-station rotary press showing positions of the cycle required to produce 1 tablet per set of tooling (courtesy Vector/Colton).

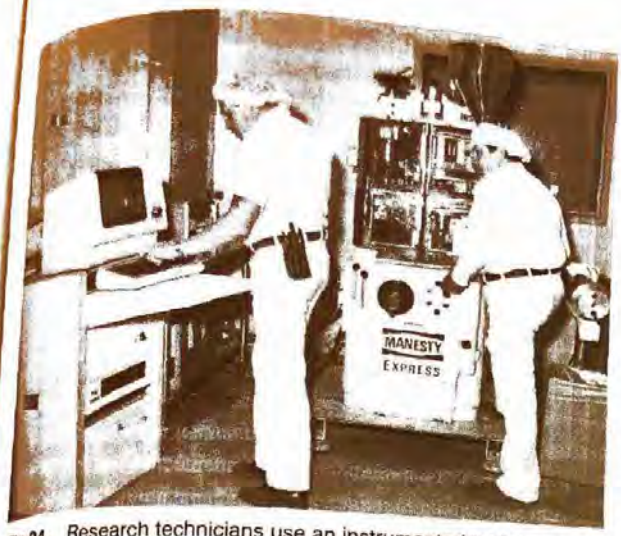


Fig 24. Research technicians use an instrumented tablet press to develop processes at Schering-Plough.

Operation of Rotary Machines

Before inserting punches and dies, make certain that the pressure has been released from the pressure wheel. The die holes should be cleaned thoroughly, making certain that the die seat is completely free of any foreign materials. Back off all die locks and loosely insert dies into the die holes, then tap each die securely into place with a fiber of soft metal rod through the upper punch holes. After all the dies have been tapped into place, tighten each die lockscrew progressively and securely. As each screw is tightened the die is checked to see that it does not project above the die table. Insert the lower punches through the hole made available by removing the punch head. Turn the machine by hand until the punch bore coincides with the plug hole. Insert each lower punch in its place progressively. Insert the upper punches by dropping them into place in the head. Each punch (upper and lower) should be coated with a thin film of mineral oil before inserting them into the machine. Adjust the ejection cam so that the lower punch is flush with the die table at the ejection point.

After insertion of the punches and dies adjust the machine for the tablet weight and hardness. The feed frame should be attached to the machine along with the feed hopper. Add a small amount of the granulation through the hopper and turn over the machine by hand. Increase the pressure by rotating the pressure wheel until a tablet is formed. Check the weight of the tablet and adjust the fill to provide the desired tablet weight. Most likely more than one adjustment of the fill will be necessary before obtaining the acceptable weight. When the fill is decreased, the pressure must be decreased to provide the same hardness in the tablet. Conversely, when the fill is increased, the pressure must be increased to obtain comparable hardness.

Fill the hopper with the granulation and turn on the power. Check tablet weight and hardness immediately after the mechanical operation begins and make suitable adjustments, if necessary. Check these properties routinely and regularly at 15- to 30-minute intervals while the machine is in operation. When the batch has been run, turn off the power. Remove the hopper and feed frame from the machine. Remove loose granulation and dust with a vacuum line. Remove all pressure from the wheel. Remove the punches and dies in the reverse order of that used in setting up the machine. First, remove the upper punches individually, then the lower punches and finally the dies. Wash each punch and die in alcohol and brush with a soft brush to remove adhering material. Dry them with a clean cloth and cover them with a thin coating of grease or oil before storing.

High-Speed Rotary Tablet Machines

The rotary tablet machine has evolved gradually into models capable of compressing tablets at high production rates. See Figs 22, 25 and 26. This has been accomplished by increasing the number of stations, ie, sets of punches and dies, in each revolution of the machine head, improvement in feeding devices, and on some models the installation of dual compression points. In Fig 26, the drawing shows a rotary machine having dual compression points. Rotary machines having dual compression points are referred to as double rotary machines, and those with one compression point, single rotary. In the diagram, half of the tablets are produced 180° from the tablet chute. They travel outside the perimeter and discharge with the second tablet production. While these models are mechanically capable of operating at the production rates shown in Table 3, the actual speed still depends on the physical characteristics of the tablet granulation and the rate which is consistent with compressed tablets having satisfactory physical characteristics. The main difficulty in rapid machine operation is assuring adequate filling of the dies. With rapid filling, dwell time of the die cavity beneath the feed frame is insufficient to ensure the requirements of uniform flow and packing of the dies. Various methods of force-feeding the granulation into the dies have been devised to refill the dies in the very short dwell time permitted on the high-speed machine. These devices are illustrated in Fig 14. Presses with triple compression points (see Table 3) permit the partial compaction of material before final compaction. This provides for the partial deaeration and particle orientation of material before final compression. This helps in the direct compacting of materials and reduces laminating and capping due to entrapped air.

Multilayer Rotary Tablet Machines

The rotary tablet machines also have been developed into models capable of producing multiple-layer tablets; the machines are able to make one-, two- or three-layer tablets [Versa Press (*Stokes/Pennwalt*)]. Stratified tablets offer a number of advantages. Incompatible drugs can be formed into a single tablet by separating the layers containing them with a layer of inert material. It has permitted the formulation of time-delay medication and offers a wide variety of possibilities in developing color combinations which give the products identity.

Originally, the tablets were prepared by a single compression method. The dies were filled with the different granulations in successive layers and the tablet was formed by a single compression stroke. The separation lines of the tablets prepared by this method tended to be irregular. In the machines now available for multilayer production the granulation receives a precompression stroke after the first and second fill, which lightly compacts the granulation and maintains a well-defined surface of separation between each layer. The operator is able to eject either precompressed layer with the machine running at any desired speed for periodic weight and analysis checks.

Other multiple-compression presses can receive previously compressed tablets and compress another granulation around the preformed tablet. An example of a press with this capability is the Manesty Drycota (*Thomas/Manesty*). Pressure coated tablets can be used to separate incompatible drug substances and also to give an enteric coating to the core tablets.

Capping and Splitting of Tablets

The splitting or capping of tablets is one of great concern and annoyance in tablet making. It is quite difficult to detect while the tablets are being processed but can be detected easily by vigorously shaking a few in the cupped hands. A slightly chipped tablet does not necessarily mean that the tablet will cap or split.

There are many factors that may cause a tablet to cap or split:

Excess "fines" or powder which traps air in the tablet mixture.

Deep markings on tablet punches. Many designs or "scores" on punches are too broad and deep. Hairline markings are just as appropriate as deep, heavy markings.

Worn and imperfect punches. Punches should be smooth and buffed. Nicked punches often will cause capping. The development of fine feather edges on tablets indicates wear on punches.

Worn dies. Dies should be replaced or reversed. Dies that are chrome-plated or have tungsten carbide inserts wear longer and give better results than ordinary steel dies.

Too much pressure. By reducing the pressure on the machines the condition may be corrected.

Table 3—Rotary Tablet Machines

Machine model	Tool sets	Maximum tablet diameter (inches)	Press speed (tablets/min)	Depth of fill (inches)
Vector-Colton equipment				
2216	16	5/8	1180	3/4
240	16	7/8	640	13/16
250	12	1 1/4	480	1 1/8
260	25	1 3/16	1450	1 3/8
	31	1	1800	1 3/8
	33	15/16	1910	1 3/8
	43	5/8	2500	1 3/8
270	25	1 3/8	450	2 3/4
Stokes/Pennwalt equipment				
Manesty equipment (Thomas Eng)				
B3B	16	5/8	350–700	11/16
	23	7/16	500–1000	11/16
BB3B	27	5/8	760–1520	11/16
	33	7/16	924–1848	11/16
	35	5/8	1490–2980	11/16
	45	7/16	1913–3826	11/16
D3B	16	1	260–520	13/16
Key equipment				
DC-16	16	15/16	210–510	13/16
BBC	27	5/8	1025–2100	11/16
	35	5/8	1325–2725	11/16
	45	7/16	1700–3500	11/16
Cadpress	37	15/16	850–3500	13/16
	45	5/8	2000–6000	11/16
	55	7/16	2500–7500	11/16
Fette equipment (Raymond Auto)		(mm)		(mm)
Perfecta 1000	28	16	2100	18
	33	13	2475	18
Perfecta 2000	29	25	2175	22
	36	16	3600	18
	43	13	4300	18
Courtoy equipment (AC Compact)				
R-100	24	25	285–2260	20
	30	19	356–2850	20
	36	13	550–440	16
Kikusui equipment				
Hercules	18	37	180–540	16
	21	26	210–630	16
	29	25	290–870	16
Virgo	19	16	418–1330	16
	24	11	528–1680	16
Killian equipment				
TX21	21	28	231–1386	20
TX25	25	22	275–2166	20
TX30	30	16	330–3150	20
TX21D	21	25	231–1826	20
TX30A	30	16	330–3150	16
TX40A	40	13	440–4200	16
Korsch equipment				
PH 250/20	20	25	240–1640	22
PH 250/25	25	16	270–2700	18
PH 250/30	30	13	315–3233	18
Elizabeth-Hata equipment				
AP-15-SSU	15	17	300–1050	8–18
AP-18-SSU	18	13	360–1260	8–18
AP-22-SSU	22	11	440–1540	8–18
AP-32-MSU	32	17	640–2240	8–18
AP-38-MSU	38	13	760–2660	8–18
AP-45-MSU	32	11	900–3150	8–18

Unsuitable formula. It may be necessary to change the formula.

Moist and soft granulation. This type of granulation will not flow freely into the dies, thus giving uneven weights and soft or capped tablets.

Poorly machined punches. Uneven punches are detrimental to the tablet machine itself and will not produce tablets of accurate weight. One punch out of alignment may cause one tablet to split or cap on every revolution.

Instrumented Tablet Presses

Compressional and ejectional forces involved in tablet compression can be studied by attaching strain gauges to the punches and other press components involved in compression.

Table 3—High-Speed Rotary Tablet Machines

Machine model	Tool sets	Maximum tablet diameter (inches)	Press speed (tablets/min)	Depth of fill (inches)
Vector-Colton equipment				
2247	33	5/8	3480	
	41	7/16	4300	3/4
	49	7/16	5150	3/4
Magna	66	22/32	10,560	3/4
	74	1/2	11,840	3/4
	90	7/16	14,400	3/4
				3/4
Stokes/Pennwalt equation				
552-2	35	5/8	800–3200	
328-4	45	3/4	1600–4500	1 1/8
610	65	7/16	3500–10,000	1 1/8
747	65	7/16	3000–10,000	1 1/8
	53	5/8	2900–8100	1 1/8
	41	15/16	2150–6150	1 1/8
Direct Triple Compression Type				
580-1	45	7/16	525–2100	
580-2	35	5/8	400–1600	11/16
610	65	7/16	3500–10,000	11/16
	53	5/8	2900–8100	11/16
Manesty equipment (Thomas Eng)				11/16
Betapress	16	5/8	600–1500	
	23	7/16	860–2160	11/16
Express	20	1	800–2000	11/16
	25	5/8	1000–2500	13/16
	30	7/16	1200–3000	11/16
Unipress	20	1	970–2420	11/16
	27	5/8	1300–3270	13/16
	34	7/16	1640–4120	11/16
Novapress	37	1	760–3700	11/16
	45	5/8	900–4500	13/16
	61	7/16	1220–6100	11/16
BB3B	35	5/8	1490–2980	11/16
BB4	27	5/8	900–2700	11/16
	35	5/8	1167–3500	11/16
	45	7/16	1500–4500	11/16
Rotapress				
Mark IIA	37	1	710–3550	13/16
	45	5/8	1640–8200	11/16
	61	7/16	2200–11,100	11/16
Mark IV	45	1	2090–6000	13/16
	55	5/8	2550–7330	11/16
	75	7/16	3500–10,000	11/16
Fette tool systems		(mm)		(mm)
PT 2080	29	25	435–2900	18
	36	16	540–4100	18
	43	16	645–4900	18
PT 2090IC	22	34	1760	18
	29	25	2900	18
	36	16	4140	18
	43	13	5160	18
	47	11	6110	18
PT 3090IC	37	34	5920	18
	49	25	7840	18
	61	16	9760	18
	73	13	16,748	18
P 3100	37	25	5618	22
	45	16	8100	18
	55	13	9900	18
Courtoy equipment (AC Compact)				
R-200	43	25	750–5833	20
	55	19	916–8500	20
	65	13	1083–10,000	16
Kikusui equipment				
Libra	36	16	900–2520	16
	45	11	1125–3150	16
	49	8	1225–3430	16
Gemini	55	16	2200–7700	16
	67	11	2680–9380	16
	73	8	2920–10,200	16
Elizabeth-Hata equipment				
AP-45-LDU	45	17	1800–6300	8–18
AP-55-LDU	55	13	2200–7700	8–18
AP-65-LDU	65	11	2600–9100	8–18
AP-71-LDU	71	11	2840–9940	8–18
51-XLDU	51	17	2040–7140	8–18
65-XLDU	61	13	2440–8540	8–18

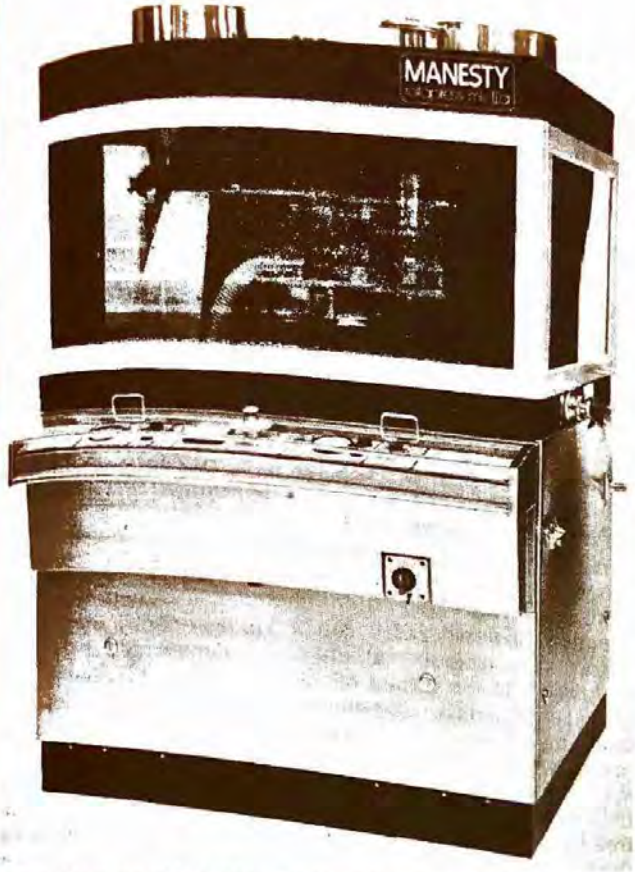


Fig 25. Rotapress Mark IIA: designed for improvements in sound reduction, operator safety, cleanliness and operational convenience; note the control panel on front of machine (courtesy, Thomas/Manesty).

The electrical output of the gauges has been monitored by telemetry or use of a dual beam oscilloscope equipped with camera.[42,43] Instrumentation permits a study of the compaction characteristics of granulations, their flowabilities and the effect of formulation additives, such as lubricants as well as differences in tablet press design, as shown in Figs 29 and 30. Physical characteristics of tablets, such as hardness, friability, disintegration time and dissolution rate, are influenced not only by the nature of the formulation but by the compressional force as well.

As can be seen in Figs 29 and 30, the rate and duration of compaction forces can be quantified. The rate of force application has a profound effect on powder consolidation within the die and, hence, efficiency of packing and powder compaction. The rate of release of force or "decompression" has a direct effect on the ability of the tablet to withstand relaxation. A prominent hypothesis, fostered by Hiestand[44,45] and later Luenberger[46] suggested that capping and laminating of tablets is caused by too-rapid stress relaxation or decompression. This explains why slowing a tablet press and using tapered dies is useful in such situations. Most prominent pharmaceutical scientists have embraced this theory and largely have discounted air entrapment as a cause of capping and laminating.

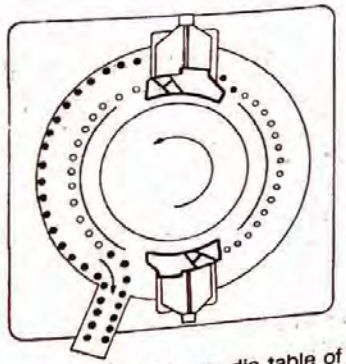


Fig 26. The movement of tablets on die table of a double rotary press (courtesy, Vector/Colton).

Fig 27. Courtoy R-100 with computer-controlled operation.

In Fig 30 an interesting set of plots is presented. Walter and Augsburger reported that as compaction force rises, the steel tooling actually compresses in accommodation to the forces applied. The forces used to produce a tablet are considerable, and should be monitored and understood.[47] Therefore, definition of the compressional force and duration of force (dwell time) giving a satisfactory tablet for a formulation provides an in-process control for obtaining both tablet-to-tablet and lot-to-lot uniformity (see Figs 24 and 31).

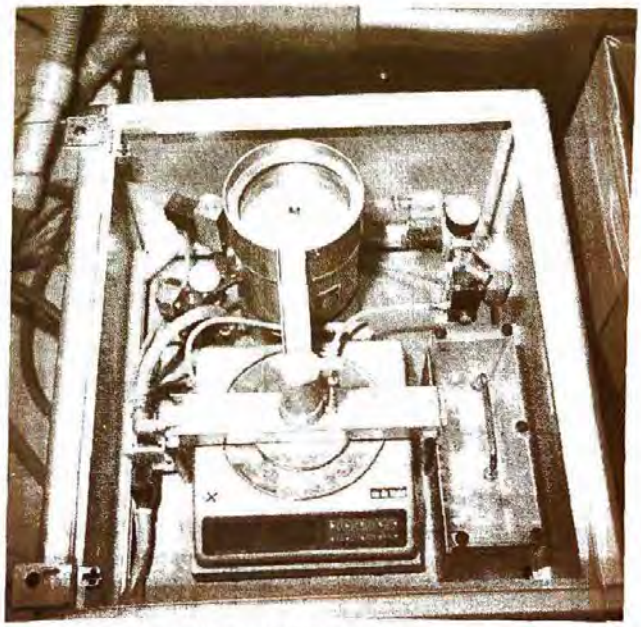


Fig 28. Direct weighing of tablets produced gives actual weight feedback for the controller of the Courtoy R-100 (seen in the bottom left of Fig 27).

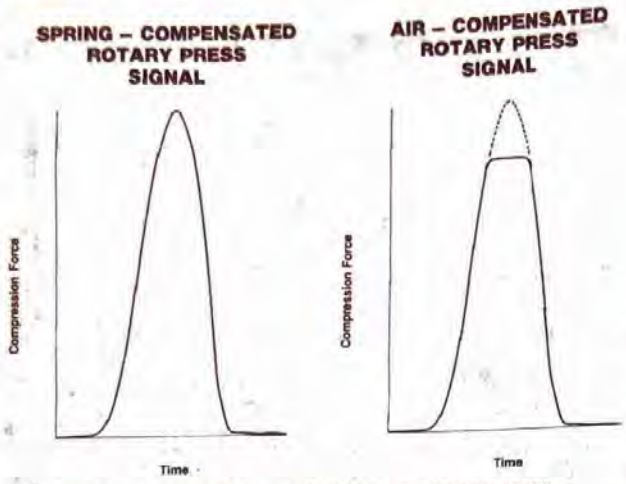


Fig 29. Force-time curves for two types of tablet press.

Instrumentation has led to the development of on-line, automatic, electromechanical tablet weight-control systems capable of continuously monitoring the weights of tablets as they are produced. Units are available commercially [Thomas Tablet Sentinel (*Thomas Eng*); Fette Compression Force Monitor (*Raymond Auto*); Vali-Tab (*Stokes/Pennwalt*)] and are applicable to single or rotary tablet machines. Most commercial presses today can be delivered with some sort of instrumentation attached. When tablet weights vary from preset limits, the monitor automatically will adjust the weight control mechanism to reestablish weights within acceptable limits. If the difficulty continues, the unit will activate an audible warning signal or an optional shut-down relay on the press (see Figs 27 and 28). Most production model tablet presses come equipped with complete instrumentation (optional) and with options for statistical analysis and print out of compression/ejection signals. The techniques and applications of press instrumentation have been reviewed.[48,49]

Contamination Control

While good manufacturing practices used by the pharmaceutical industry for many years have stressed the importance of cleanliness of equipment and facilities for the manufacture of drug products, the penicillin contamination problem resulted in renewed emphasis on this aspect of manufacturing. Penicillin, either as an airborne dust or residual quantities remaining in equipment, is believed to have contaminated unrelated products in sufficient concentrations to cause allergic reactions in individuals, hypersensitive to penicillin,

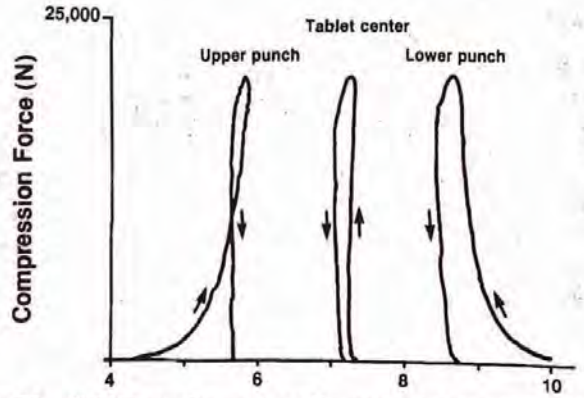


Fig 30. Plot showing the upper and lower punch forces as functions of the position of the punch face within the die. A biaxial force/displacement curve also shown is a plot of the position of the tablet center as a function of the compress ion force.

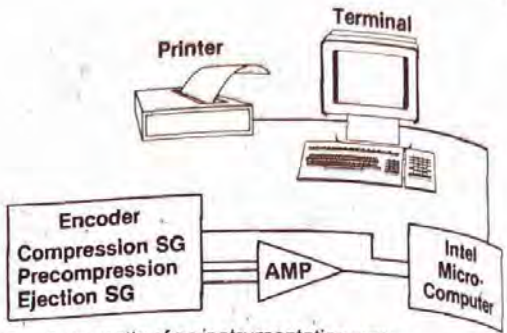


Fig 31. Schematic of an instrumentation system using a microcomputer as developed by Schering-Plough.

who received these products. This resulted in the industry spending millions of dollars to change or modify buildings, manufacturing processes, equipment and standard operating procedures to eliminate penicillin contamination.

With this problem has come renewed emphasis on the dust problem, material handling and equipment cleaning in dealing with drugs, especially potent chemicals. Any process using chemicals in powder form can be a dusty operation; the preparation of compressed tablets and encapsulation falls in this category. In the design of tablet presses attention is being given to the control and elimination of dust generated in the tableting process. In the Perfecta press shown in Fig 32, the pressing compartment is completely sealed off from the outside environment, making cross-contamination nearly impossible. The pressing compartment can be kept dust-free by the air supply and vacuum equipment developed for the machine. It removes airborne dust and granular particles which have not been compressed, thus keeping the circular pressing compartment and the upper and lower punch guides free of dust.

Drug manufacturers have the responsibility to make certain that microorganisms present in finished products are unlikely

Fig 32. Fette Perfecta 3000 high-speed tablet press with pressing compartment completely sealed off from outside environment making cross contamination impossible (courtesy, Raymond Auto).

to cause harm to the patient and will not be deleterious to the product. An outbreak of *Salmonella* infections in Scandinavian countries was traced to thyroid tablets which had been prepared from contaminated thyroid powder. This concern eventually led to the establishment of microbial limits for raw materials of animal or botanical origin, especially those that readily support microbial growth and are not rendered sterile during subsequent processing. Harmful microorganisms when present in oral products include *Salmonella* spp, *E coli*, certain *Pseudomonas* spp such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The compendia have microbial limits on raw materials such as aluminum hydroxide gel, corn starch, thyroid, acacia and gelatin.

These represent examples of the industry's efforts to conform with the intent of current good manufacturing practice as defined by the FDA.

Tablet Formulations

Wet Granulation

CT Acetaminophen, 300 mg

Ingredients	In each	In 10,000
Acetaminophen	300 mg	3000 g
Polyvinylpyrrolidone	22.5 mg	225 g
Lactose	61.75 mg	617.5 g
Alcohol SD3A—200 proof	4.5 mL	45 L
Stearic acid	9 mg	90 g
Talc	13.5 mg	135 g
Corn starch	43.25 mg	432.5 g

Blend acetaminophen, polyvinylpyrrolidone and lactose together; pass through a 40-mesh screen. Add the alcohol slowly and knead well. Screen the wet mass through a 4-mesh screen. Dry the granulation at 50° overnight. Screen the dried granulation through a 20-mesh screen. Bolt the stearic acid, talc and corn starch through a 60-mesh screen prior to mixing by tumbling with the granulation. Compress, using 7/16-inch standard concave punch. 10 tablets should weigh 4.5 g (courtesy, Abbott).

CT Ascorbic Acid USP, 50 mg

Ingredients	In each	In 7000
Ascorbic acid USP (powder No. 80)[a]	55 mg	385 g
Lactose	21 mg	147 g
Starch (potato)	13 mg	91 g
Ethylcellulose N 100 (80–105 cps)	16 mg	112 g
Starch (potato)	7 mg	49 g
Talc	6.5 mg	45.5 g
Calcium stearate (impalpable powder)	1 mg	7 g
Weight of granulation		836.5 g

[a] Includes 10% in excess of claim.

Granulate the first three ingredients with ethylcellulose (5%) dissolved in anhydrous ethyl alcohol adding additional anhydrous alcohol to obtain good, wet granules. Wet-screen through a #8 stainless-steel screen and dry at room temperature in an air-conditioned area. Dry-screen through a #20 stainless-steel screen and incorporate the remaining three ingredients. Mix thoroughly and compress. Use a flat, beveled 1/4-inch punch. 20 tablets should weigh 2.39 g.

Chewable Antacid Tablets

Ingredients	In each	In 10,000
Magnesium trisilicate	500 mg	5000 g
Aluminum hydroxide, dried gel	250 mg	2500 g
Mannitol	300 mg	3000 g
Sodium saccharin	2 mg	20 g
Starch paste, 5%	qs	qs
Oil of peppermint	1 mg	10 g
Magnesium stearate	10 mg	100 g
Corn starch	10 mg	100 g

Mix the magnesium trisilicate and aluminum hydroxide with the mannitol. Dissolve the sodium saccharin in a small quantity of purified water, then combine this with the starch paste. Granulate the powder blend with the starch paste. Dry at 140°F and screen through 16-mesh screen. Add the flavoring oil, magnesium stearate and corn starch; mix well. Age the granulation for at least 24 hours and compress, using a 5/8-inch flat-face bevel-edge punch (courtesy, Atlas).

CT Hexavitamin

Ingredients	In each	In 7000
Ascorbic acid USP (powder)[a]	82.5 mg	577.5 g
Thiamine mononitrate USP (powder)[a]	2.4 mg	16.8 g
Riboflavin[a]	3.3 mg	23.1 g
Nicotinamide USP (powder)[a]	22 mg	154 g
Starch	13.9 mg	97.4 g
Lactose	5.9 mg	41.2 g
Zein	6.4 mg	45 g
Vitamin A acetate:	6250 U	
Vitamin D_2[a] (use Pfizer crystalets medium granules containing 500,000 U vitamin A acetate and50,000 U vitamin D_2/g).	625 U	87.5 g
Magnesium stearate		7.5 g
Weight of granulation		1050 g

[a] Includes the following in excess of claim: ascorbic acid 10%, thiamine mononitrate 20%, riboflavin 10%, nicotinamide 10% and vitamin A acetate–vitamin D_2 crystalets 25%.

Thoroughly mix the first six ingredients and granulate with zein (10% in ethyl alcohol, adding additional alcohol if necessary to obtain good, wet granules). Wet-screen through a #8 stainless-steel screen and dry at 110 to 120°F. Dry-screen through a #20 stainless-steel screen and add the vitamin crystalets. Mix thoroughly, lubricate and compress. 10 tablets should weigh 1.50 g. Coat with syrup.

CT Theobromine–Phenobarbital

Ingredients	In each	In 7000
Theobromine	325 mg	2275 g
Phenobarbital	33 mg	231 g
Starch	39 mg	273 g
Talc	8 mg	56 g
Acacia (powder)	8 mg	56 g
Stearic acid	0.7 mg	4.9 g
Weight of granulation		2895.9 g

Prepare a paste with the acacia and an equal weight of starch. Use this paste for granulating the theobromine and pheno- barbital. Dry and put through a 12-mesh screen, add the remainder of the material, mix thoroughly and compress into tablets, using a 13/32-inch concave punch. 10 tablets should weigh 4.13 g.

Fluid-Bed Granulation

CT Ascorbic Acid USP, 50 mg

Ingredients	In each	In 10,0000
Ascorbic acid USP (powder no 80)[a]	55 mg	550 g
Lactose	21 mg	210 g
Starch (potato)	13 mg	130 g
Ethylcellulose N100 (80-105 cps)	16 mg	160 g
Starch (potato)	7 mg	70 g
Talc	6.5 mg	65 g
Calcium stearate	1 mg	10 g
Weight of granulation		1195.0 g

[a] Includes 10% in excess of claim.

Add the first three ingredients to the granulator. Mix for 5 to 15 minutes or until well mixed. Dissolve the ethylcellulose in anhydrous ethanol and spray this solution, and any additional ethanol, into the fluidized mixture. Cease spraying when good granules are produced. Dry to approximately 3% moisture. Remove the granules and place them in a suitable blender. Sequentially add the remaining three ingredients with mixing steps in between each addition. Compress, using a flat, beveled, ¼-inch punch. 20 tablets should weigh 2.39 g.

Sustained-Release (SR) Procainamide tablets

Ingredients	In each	In 10,000
Procainamide	500 mg	5000 g
HPMC 2208, USP	300 mg	3000 g
Carnauba wax	60 mg	600 g
HPMC 2910, USP	30 mg	300 g
Magnesium stearate	4 mg	40 g
Stearic acid	11 mg	110 g
Talc	5 mg	50 g
Weight of granulation		9100 g

Place the first three ingredients in the granulator and mix for 5 to 15 minutes. Dissolve the HPMC in water (mix in hot water, then cool down) and spray into the fluidized mixture. Dry to approximately 5% moisture. Sequentially add the last three ingredients with mixing steps in between each addition. Compress, using capsule-shaped tooling. 10 tablets should weigh 9.1 g.

Dry Granulation

CT Acetylsalicylic Acid

Ingredients	In each	In 7000
Acetylsalicylic Acid (crystals 20-mesh)	0.325 g	2275 g
Starch		226.8 g
Weight of granulation		2501.8 g

Dry the starch to a moisture content of 10%. Thoroughly mix this with the acetylsalicylic acid. Compress into slugs. Grind the slugs to 14- to 16-mesh size. Recompress into tablets, using a 13/32-inch punch. 10 tablets should weigh 3.575 g.

CT Sodium Phenobarbital

Ingredients	In each	In 7000
Phenobarbital sodium	65 mg	455 g
Lactose (granular, 12-mesh)	26 mg	182 g
Starch	20 mg	140 g
Talc	20 mg	140 g
Magnesium stearate	0.3 mg	2.1 g
Weight of granulation		919.1 g

Mix all the ingredients thoroughly. Compress into slugs. Grind and screen to 14- to 16-mesh granules. Recompress into tablets, using a 9/32-inch concave punch. 10 tablets should weigh 1.3 g.

CT Vitamin B Complex

Ingredients	In each	In 10,000
Thiamine mononitrate[a]	0.733 mg	7.33 g
Riboflavin[a]	0.733 mg	7.33 g
Pyridoxine hydrochloride	0.333 mg	3.33 g
Calcium pantothenate[a]	0.4 mg	4 g
Nicotinamide	5 mg	50 g
Lactose (powder)	75.2 mg	752 g
Starch	21.9 mg	219 g
Talc	20 mg	200 g
Stearic acid (powder)	0.701 mg	7.01 g
Weight of granulation		1250 g

[a] Includes 10% in excess of claim.

Mix all the ingredients thoroughly. Compress into slugs. Grind and screen to 14- to 16-mesh granules. Recompress into tablets, using a ¼-inch concave punch. 10 tablets should weigh 1.25 g.

Sufficient tartaric acid should be used in these tablets to adjust the pH to 4.5.

Direct Compression

APC Tablets

Ingredients	In each	In 10,000
Aspirin (40-mesh crystal)	224 mg	2240 g
Phenacetin	160 mg	1600 g
Caffeine (anhyd USP gran)	32 mg	320 g
Compressible sugar (Di-Pac[a])	93.4 mg	934 g
Sterotex	7.8 mg	78 g
Silica gel (Syloid 244[b])	2.8 mg	28 g

[a] Amstar.
[b] Davison Chem.

Blend ingredients in a twin-shell blender for 15 minutes and compress on a 13/32-inch standard concave punch (courtesy, Amstar).

CT Ascorbic Acid USP, 250 mg

Ingredients	In each	In 10,000
Ascorbic Acid USP (Merck, fine crystals)	255 mg	2550 g
Microcrystalline cellulose[a]	159 mg	1590 g
Stearic acid	9 mg	90 g
Colloidal silica[b]	2 mg	20 g
Weight of granulation		4250 g

[a] Avicel-PH-101.
[b] Cab-O-Sil.

Blend all ingredients in a suitable blender. Compress, using 7/16-inch standard concave punch. 10 tablets should weigh 4.25 g (courtesy FMC).

Breath Freshener Tablets

Ingredients	In each	In 10,000
Wintergreen oil	0.6 mg	6 g
Menthol	0.85 mg	8.5 g
Peppermint oil	0.3 mg	3 g
Silica gel (Syloid 244[a])	1 mg	10 g
Sodium saccharin	0.3 mg	3 g
Sodium bicarbonate	14 mg	140 g
Mannitol USP (granular)	180.95 mg	1809.5 g
Calcium stearate	2 mg	20 g

[a] Davison Chem.

Mix the flavor oils and menthol until liquid. Adsorb onto the silica gel. Add the remaining ingredients. Blend and compress on 5/16-in flat-face bevel-edge punch to a thickness of 3.1 mm (courtesy, Atlas).

Chewable Antacid Tablets

Ingredients	In each	In 10,000
Aluminum hydroxide and magnesium carbonate, co-dried gel[a]	325 mg	3250 g
Mannitol USP (granular)	675 mg	6750 g
Microcrystalline cellulose[b]	75 mg	750 g
Corn starch	30 mg	300 g
Calcium stearate	22 mg	220 g
Flavor	qs	qs

[a] Reheis F-MA-11.
[b] Avicel.

Blend all ingredients in a suitable blender. Compress, using a 5/8-inch flat-face bevel-edge punch (courtesy, Atlas).

Chewable Multivitamin Tablets

Ingredients	In each	In 10,000
Vitamin A USP (dry, stabilized form)	5000 USP units	50 million units
Vitamin D (dry, stabilized form)	400 USP units	4 million units
Ascorbic Acid USP	60.0 mg	600 g
Thiamine Hydrochloride USP	1 mg	10 g
Riboflavin USP	1.5 mg	15 g
Pyridoxine Hydrochloride USP	1 mg	10 g
Cyanocobalamin USP	2 μg	20 mg
Calcium Pantothenate USP	3 mg	30 g
Niacinamide USP	10 mg	100 g
Mannitol USP (granular)	236.2 mg	2362 g
Corn starch	16.6 mg	166 g
Sodium saccharin	1.1 mg	11 g
Magnesium stearate	6.6 mg	66 g
Talc USP	10 mg	100 g
Flavor	qs	qs

Blend all ingredients in a suitable blender. Compress, using a 7/16-inch flat-face bevel-edge punch (courtesy, Atlas).

CT Ferrous Sulfate

Ingredients	In each	In 7000
Ferrous Sulfate USP (crystalline)	0.325 g	2275 g
Talc		0.975 g
Sterotex		1.95 g
Weight of granulation		2277.93 g

Grind to 12- to 14-mesh, lubricate and compress. Coat immediately to avoid oxidation to the ferric state with 0.410 gr of tolu balsam (dissolved in alcohol) and 0.060 gr of salol and chalk. Use a deep, concave, 11/32-inch punch. 10 tablets should weigh 3.25 g.

CT Methenamine

Ingredients	In each, g	In 7000, g
Methenamine (12- to 14-mesh crystals)	0.325	2275
Weight of granulation		2275

Compress directly, using a 7/16-inch punch. 10 tablets should weigh 3.25 g.

CT Phenobarbital USP, 30 mg

Ingredients	In each	In 10,000
Phenobarbital	30.59 mg	305.9 g
Microcrystalline cellulose[a]	30.59 mg	305.9 g
Spray-dried lactose	69.16 mg	691.6 g
Colloidal silica[b]	1.33 mg	13.3 g
Stearic acid	1.33 mg	13.3 g
Weight of granulation		1330 g

[a] Avicel-PH-101.
[b] QUSO F-22.

Screen the phenobarbital to break up lumps and blend with the microcrystalline cellulose. Add spray-dried lactose and blend. Finally, add the stearic acid and colloidal silica; blend to obtain a homogeneous mixture. Compress, using a 9/32-inch shallow concave punch. 10 tablets should weigh 1.33 g (courtesy, FMC).

Molded Tablets or Tablet Triturates (TT)

Tablet triturates are small, discoid masses of molded powders weighing 30 to 250 mg each. The base consists of lactose, β-lactose, mannitol, dextrose or other rapidly soluble materials. It is desirable in making tablet triturates to prepare a solid dosage form which is rapidly soluble; as the result they are generally softer than compressed tablets.

This type of dosage form is selected for a number of drugs because of its rapidly dissolving characteristic. Nitroglycerin in many concentrations is prepared in tablet triturate form since the molded tablet rapidly dissolves when administered by placing under the tongue. Potent alkaloids and highly toxic drugs used in small doses are prepared as tablet triturates which can serve as dispensing tablets to be used as the source of the drug in compounding other formulations or solutions. Narcotics in the form of hypodermic tablets originally were made as tablet triturates because they rapidly dissolve in sterile water for injection prior to administration. Today with stable injections of narcotics available, there is no longer any justification for their use in this manner. Although many hypodermic tablets currently are made, they are used primarily for oral administration.

Tablet triturates are made by forcing a moistened blend of the drug and diluent into a mold, extruding the formed mass, which is allowed to dry. This method is essentially the same as it was when introduced by Fuller in 1878. Hand molds may vary in size but the method of operation is essentially the same. Molds consist of two plates made from polystyrene plastic, hard rubber, nickel-plated brass or stainless steel. The mold plate contains 50 to 500 carefully polished perforations. The other plate is fitted with a corresponding number of projecting pegs or punches which fit the perforations in the mold plate. The mold plate is placed on a flat surface, the moistened mass is forced into the perforations and the excess is scraped from the top surface. The mold plate is placed over the plate with the corresponding pegs and lowered. As the plates come together, the pegs force the

tablet triturates from the molds. They remain on the tops of the pegs until dry and they can be handled (see Fig 33). In some hand molds, as shown in Fig 34, the pegs are forced down onto the plate holding the moist trituration.

Formulation

In developing a formula it is essential that the blank weight of the mold which is to be used is known. To determine this, the weight of the diluent which exactly fills all the openings in the mold is determined by experiment. This amount of diluent is weighed and placed aside. The total amount of the drug required is determined by multiplying the number of perforations in the plate used in the previous experiment by the amount of drug desired in each tablet. The comparative bulk of this medication is compared with that of an equal volume of diluent and that quantity of diluent is removed and weighed. The drug and the remaining diluent are mixed by trituration, and the resulting triturate is moistened and forced into the openings of the mold. If the perforations are not filled completely, more diluent is added, its weight noted and the formula written from the results of the experiments.

It is also permissible in the development of the formula to weigh the quantity of medication needed for the number of tablets represented by the number of perforations in the mold, triturate with a weighed portion (more than ½) of the diluent, moisten the mixture and press it into the perforations of the mold. An additional quantity of the diluent is moistened immediately and also forced into the perforations in the plate until they are filled completely. All excess diluent is removed, the trial tablets are forced from the mold, then triturated until uniform, moistened again, if necessary, and remolded. When these tablets are dried thoroughly and weighed, the difference between their total weight and the weight of medication taken will indicate the amount of diluent required and accordingly supply the formula for future use for that particular tablet triturate.

For proper mixing procedures of the medication with the diluent see Chapter 91.

Preparation

The mixed powders are moistened with a proper mixture of alcohol and water, although other solvents or moistening agents such as acetone, petroleum benzin and various combinations of these may be used in specific cases; the agent of choice depends on the solvent action which it will exert on the powder mixture. Often the moistening agent is 50% alcohol, but this concentration may be increased or decreased depending on the constituents of the formula. Care must be used in adding the solvent mixture to the powder. If too much is used, the mass will be soggy, will require a long time to dry and the finished tablet will be hard and slowly soluble; if the mass is too wet, shrinkage will occur in the molded tablets; finally a condition known as creeping will be noticed. Creeping is the concentration of the medication on the surface of the tablet caused by capillarity and rapid evaporation of the solvent from the surface. Because molded tablets by their very nature are quite friable, an inaccurate strength in each tablet may result from creeping if powder is lost from the tablet's surface. On the other hand, if an insufficient amount of moistening agent is used, the mass will not have the proper cohesion to make a firm tablet. The correct amount of moistening agent can be determined initially only by experiment.

Fig 33. Hand-molding tablet triturates (courtesy, MSD).

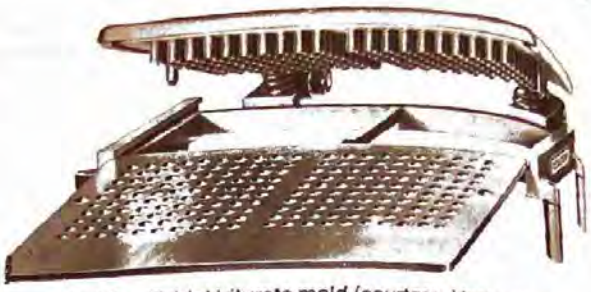


Fig 34. Tablet triturate mold (courtesy, Vector/Colton).

Hand-Molding Tablet Triturates

In preparing hand-molded tablets place the mold plate on a glass plate. The properly moistened material is pressed into the perforations of the mold with a broad spatula exerting uniform pressure over each opening. The excess material is removed by passing the spatula at an oblique angle with strong hand pressure over the mold to give a clean, flat surface. The material thus removed should be placed with the remainder of the unmolded material.

The mold with the filled perforations should be reversed and moved to another clean part of the plate where the pressing operation with the spatula is repeated. It may be necessary to add more material to fill the perforations completely and uniformly. The mold should be allowed to stand in a position so that part of the moistening agent will evaporate equally from both faces. While the first plate is drying, another mold can be prepared. As soon as the second mold has been completed, the first mold should be sufficiently surface-dried so that the pegs will press the tablets from the mold with a minimum of sticking.

To remove the tablets from the mold, place the mold over the peg plate so that the pegs and the perforations are in juxtaposition. The tablets are released from the mold by hand pressure, which forces the pegs through the perforations. The ejected tablets are spread evenly in single layers on silk trays and dried in a clean, dust-free chamber with warm circulating air. If only a small quantity of tablet triturates is made and no warm-air oven is available, the tablet triturates may be dried to constant weight at room temperature.

Machine-Molding Tablet Triturates

Tablet triturates also can be made using mechanical equipment. The automatic tablet triturate machine illustrated in Fig 35 makes tablet triturates at a rate of 2500/minute. For machine-molding, the powder mass need not be as moist as for plate-molding since the time interval between forming the tablets and pressing them is considerably shorter. The moistened mass passes through the funnel of the hopper to the feed plates below. In this feed plate are four holes having the same diameter as the mouth of the funnel. The material fills one hole at a time and, when filled,

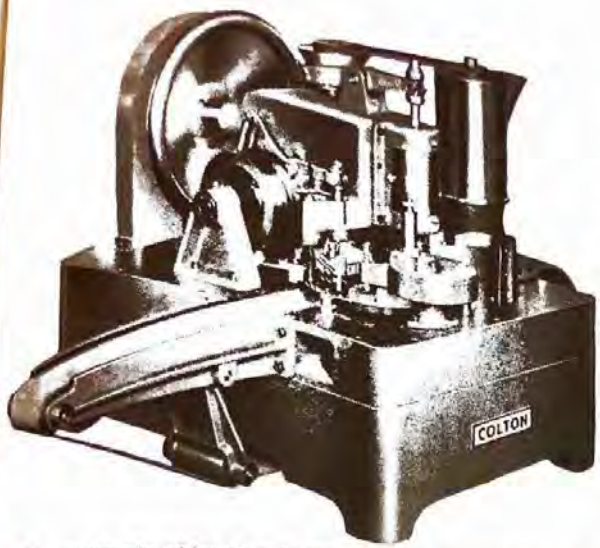


Fig 35. Automatic tablet triturate machine (courtesy, Vector-Colton).

revolves to a position just over the mold plate. When in position the weighted pressure foot lowers and imprisons the powder. At the same time a spreader in the sole of the pressure foot rubs it into the mold cavities and evens it off so that the triturates are smooth on the surface and are of uniform density. When this operation is completed, the mold passes to the next position, where it registers with a nest of punches or pegs which eject the tablets from the mold plate onto a conveyor belt. The conveyor belt sometimes is extended to a length of 8 or 10 feet under a battery of infrared drying lamps to hasten the setting of the tablets for more rapid handling. This method of drying can be used only if the drug is chemically stable to these drying conditions.

Compressed Tablet Triturates

Frequently, tablet triturates are prepared on compression tablet machines using flat-face punches. When solubility and a clear solution are required, water-soluble lubricants must be used to prevent sticking to the punches. The granulations are prepared as directed for ordinary compressed tablets; lactose generally is used as the diluent. Generally, tablet triturates prepared by this method are not as satisfactory as the molded type regarding their solubility and solution characteristics.

Tablet Characteristics

Compressed tablets may be characterized or described by a number of specifications. These include the diameter size, shape, thickness, weight, hardness, disintegration time and dissolution characteristics. The diameter and shape depend on the die and the punches selected for the compression of the tablet. Generally, tablets are discoid in shape, although they may be oval, oblong, round, cylindrical or triangular. Their upper and lower surfaces may be flat, round, concave or convex to various degrees. The concave punches (used to prepare convex tablets) are referred to as shallow, standard and deep cup, depending on the degree of concavity (see Figs 17–20). The tablets may be scored in halves or quadrants to facilitate breaking if a smaller dose is desired. The top or lower surface may be embossed or engraved with a symbol or letters which serve as an additional means of identifying the source of the tablets. These characteristics along with the color of the tablets tend to make them distinctive and identifiable with the active ingredient which they contain.

The remaining specifications assure the manufacturer that the tablets do not vary from one production lot to another. In the case of new tablet formulations their therapeutic efficacy is demonstrated through clinical trials, and it is the manufacturer's aim to reproduce the same tablet with the exact characteristics of the tablets which were used in the clinical evaluation of the dosage form. Therefore, from the control viewpoint these specifications are important for reasons other than physical appearance.

Tablet Hardness

The resistance of the tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. In the past, a rule of thumb describes a tablet to be of proper hardness if it is firm enough to break with a sharp snap when it is held between the 2nd and 3rd fingers and using the thumb as the fulcrum, yet doesn't break when it falls on the floor. For obvious reasons and control purposes a number of attempts have been made to quantitate the degree of hardness.

A small and portable hardness tester was manufactured and introduced in the mid-1930s by *Monsanto*. It now is distributed by the Stokes Div (*Pennwalt*) and may be designated as either the Monsanto or Stokes hardness tester. The instrument measures the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet. The force is measured in kilograms and when used in production, a hardness of 4 kg is considered to be minimum for a satisfactory tablet.

The Strong-Cobb hardness tester introduced in 1950 also measures the diametrically applied force required to break the tablet. In this instrument the force is produced by a manually operated air pump. As the pressure is increased, a plunger is forced against the tablet placed on anvil. The final breaking point is indicated on a dial calibrated into 30 arbitrary units. The hardness values of the Stokes and Strong-Cobb instruments are not equivalent. Values obtained with the Strong-Cobb tester have been found to be 1.6 times those of the Stokes tester.

Another instrument is the Pfizer hardness tester which operates on the same mechanical principle as ordinary pliers. The force required to break the tablet is recorded on a dial and may be expressed as either kilograms or pounds of force. In an experimental comparison of testers the Pfizer and the Stokes testers were found to check each other fairly well. Again the Strong-Cobb tester was found to give values 1.4 to 1.7 times the absolute values on the other instruments.

The most widely used apparatus to measure tablet hardness or crushing strength is the Schleuniger apparatus, also known as the Heberlein, distributed by *Vector*. This, and other newer electrically operated test equipment, eliminates the operator variability inherent in the measurements described above. Newer equipment is also available with printers to provide a record of test results. See Fig 36.

Manufacturers, such as *Key*, *Van Kel*, *Erweka* and others make similar hardness testers.

Hardness (or more appropriately, crushing strength) determinations are made throughout the tablet runs to determine the need for pressure adjustments on the tableting machine. If the tablet is too hard, it may not disintegrate in the required period of time or meet the dissolution specification; if it is too soft, it will not withstand the handling during subsequent processing such as coating or packaging and shipping operations.

A tablet property related to hardness is *friability*, and the measurement is made by use of the Roche friabilator. Rather than a measure of the force required to crush a tablet, the instrument is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. A number of tablets are weighed and placed in the tumbling apparatus where they are exposed to rolling and repeated

Fig 36. The Schleuniger or Heberlein tablet hardness tester shown with calibration blocks (courtesy, Vector).

shocks resulting from freefalls within the apparatus. After a given number of rotations the tablets are weighed, and the loss in weight indicates the ability of the tablets to withstand this type of wear (Fig 37).

Recent research has proposed that there are at least three measurable hardness parameters that can give a clue to the compatibility and intrinsic strength of powdered materials. These include bonding strength, internal strain and brittleness. Hiestand proposed indeces to quantify these parameters and they are listed in Table 4 for a number of materials.

The higher the bonding index, the stronger a tablet is more likely to be. The higher the strain index, the weaker the tablet. Since the two parameters are opposite in their effect on the tablet, it is possible for a material (such as Avicel) to have a relatively high strain index, but yet have superior compaction properties because of an extraordinary bonding potential. The higher the brittleness index, the more friable the tablet is likely to be. For a more detailed discussion of this subject, the reader is directed to Refs 22, 37, 38.

A similar approach is taken by many manufacturers when they evaluate a new product in the new market package by sending the package to distant points and back using various methods of transportation. This is called a "shipping test." The condition of the product on its return indicates its ability to withstand transportation handling.

Tablet Thickness

The thickness of the tablet from production-run to production-run is controlled carefully. Thickness can vary with no

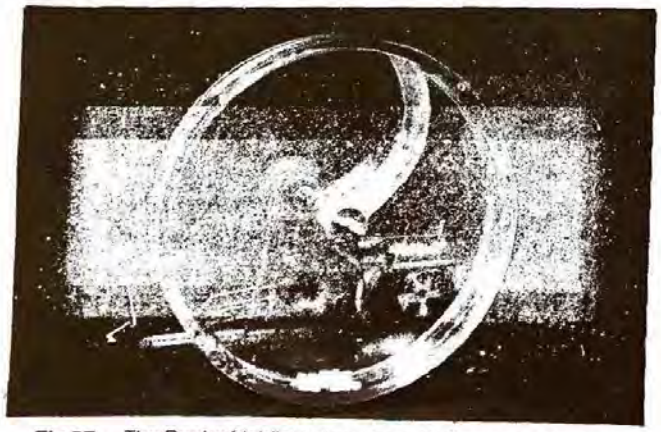


Fig 37. The Roche friabilator (courtesy, Hoffmann-LaRoche).

Table 4—Hiestand Compaction Indices for a Number of Materials

Material	Bonding index	Strain index	Brittleness index
Aspirin	1.5	1.11	0.16
Dicalcium phosphate	1.3	1.13	0.15
Lactose anhydrous	0.8	1.40	0.27
Avicel pH 102	4.3	2.20	0.04
Corn starch	0.4	2.48	0.25
Sucrose NF	1.0	1.45	0.35
Erythromycin dihydrate	1.9	2.13	0.98

change in weight due to difference in the density of the granulation and the pressure applied to the tablets, as well as the speed of tablet compression. Not only is the tablet thickness important in reproducing tablets identical in appearance but also to insure that every production lot will be usable with selected packaging components. If the tablets are thicker than specified, a given number no longer may be contained in the volume of a given size bottle. Tablet thickness also becomes an important characteristic in counting tablets using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. A column containing a known number of tablets is measured for height; filling is accomplished by continually dropping columns of tablets of the same height into bottles. If thickness varies throughout the lot, the result will be variation in count. Other pieces of filling equipment can malfunction due to variation in tablet thickness since tablets above specified thickness may cause wedging of tablets in previously adjusted depths of the counting slots. Tablet thickness is determined with a caliper or thickness gauge which measures the thickness in millimeters. A plus or minus 5% may be allowed depending on the size of the tablet.

Uniformity of Dosage Forms

Tablet Weight—The volumetric fill of the die cavity determines the weight of the compressed tablet. In setting up the tablet machine the fill is adjusted to give the desired tablet weight. The weight of the tablet is the quantity of the granulation which contains the labeled amount of the therapeutic ingredient. After the tablet machine is in operation the weights of the tablets are checked routinely either manually or electronically to insure that proper-weight tablets are being made. This has become rather routine in most manufacturing operations with newer electronically controlled tablet presses. The USP has provided tolerances for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50 mg or more of the drug substance or when the latter comprises 50% or more, by weight, of the dosage form. Twenty tablets are weighed individually and the average weight is calculated. The variation from the average weight in the weights of not more than two of the tablets must not differ by more than the percentage listed below; no tablet differs by more than double that percentage. Tablets that are coated are exempt from these requirements but must conform to the test for content uniformity if it is applicable.

Average weight	Percentage difference
130 mg or less	10
More than 130 mg through 324 mg	7.5
More than 324 mg	5

Content Uniformity—In order to ensure that every tablet contains the amount of drug substance intended, with little

variation among tablets within a batch, the USP includes the content uniformity test for certain tablets. Due to the increased awareness of physiological availability, the content uniformity test has been extended to monographs on all coated and uncoated tablets and all capsules intended for oral administration where the range of sizes of the dosage form available includes a 50 mg or smaller size, in which case the test is applicable to all sizes (50 mg and larger and smaller) of that tablet or capsule. The official compendia can be consulted for the details of the test. Tablet monographs with a content uniformity requirement do not have a weight variation requirement.

Tablet Disintegration

It is recognized generally that the *in vitro* tablet disintegration test does not necessarily bear a relationship to the *in vivo* action of a solid dosage form. To be absorbed, a drug substance must be in solution and the disintegration test is a measure only of the time required under a given set of conditions for a group of tablets to disintegrate into particles. Generally, this test is useful as a quality-assurance tool for conventional (nonsustained-release) dosage forms. In the present disintegration test the particles are those which will pass through a 10-mesh screen. In a comparison of disintegration times and dissolution rates or initial absorption rates of several brands of aspirin tablets, it was found that the faster absorbed tablets had the longer disintegration time. Regardless of the lack of significance as to *in vivo* action of the tablets, the test provides a means of control in assuring that a given tablet formula is the same as regards disintegration from one production batch to another. The disintegration test is used as a control for tablets intended to be administered by mouth, except where tablets are intended to be chewed before being swallowed or where tablets are designed to release the drug substance over a period of time.

Exact specifications are given for the test apparatus inasmuch as a change in the apparatus can cause a change in the results of the test. The apparatus consists of a basket rack holding six plastic tubes, open at the top and bottom; the bottom of the tubes is covered with 10-mesh screen. See Fig 38. The basket rack is immersed in a bath of suitable liquid, held at 37°, preferably in a 1-L beaker. The rack moves up and down in the fluid at a specified rate. The volume of the fluid is such that on the upward stroke the wire mesh remains at least 2.5 cm below the surface of the fluid and descends to not less than 2.5 cm from the bottom on the downward stroke. Tablets are placed in each of the six cylinders along with a plastic disc over the tablet unless otherwise directed in the monograph. The end-point of the test is indicated when any residue remaining is a soft mass having no palpably soft core. The plastic discs help to force any soft mass which forms through the screen.

For compressed uncoated tablets the testing fluid is usually water at 37°, but in some cases the monographs direct that Simulated Gastric Fluid TS be used. If one or two tablets fail to disintegrate, the test is to be repeated using 12 tablets. Of the 18 tablets then tested, 16 must have disintegrated within the given period of time. The conditions of the test are varied somewhat for coated tablets, buccal tablets and sublingual tablets. Disintegration times are included in the individual tablet monograph. For most uncoated tablets the period is 30 minutes although the time for some uncoated tablets varies greatly from this. For coated tablets up to 2 hours may be required, while for sublingual tablets, such as CT Isoproterenol Hydrochloride, the disintegration time is 3 minutes. For the exact conditions of the test, consult the USP.

Dissolution Test

For certain tablets the monographs direct compliance with limits on dissolution rather than disintegration. Since drug absorption and physiological availability depend on having the drug substance in the dissolved state, suitable dissolution characteristics are an important property of a satisfactory tablet. Like the disintegration test, the dissolution test for measuring the amount of time required for a given percentage of the drug substance in a tablet to go into solution under a specified set of conditions is an *in vitro* test. It is intended to provide a step towards the evaluation of the physiological availability of the drug substance, but as described currently, it is not designed to measure the safety or efficacy of the tablet being tested. Both the safety and effectiveness of a specific dosage form must be demonstrated initially by means of appropriate *in vivo* studies and clinical evaluation. Like the disintegration test, the dissolution test does provide a means of control in assuring that a given tablet formulation is the same as regards dissolution as the batch of tablets shown initially to be clinically effective. It also provides an *in vitro* control procedure to eliminate variations among production batches. Refer to Chapter 34 for a complete discussion of dissolution testing.

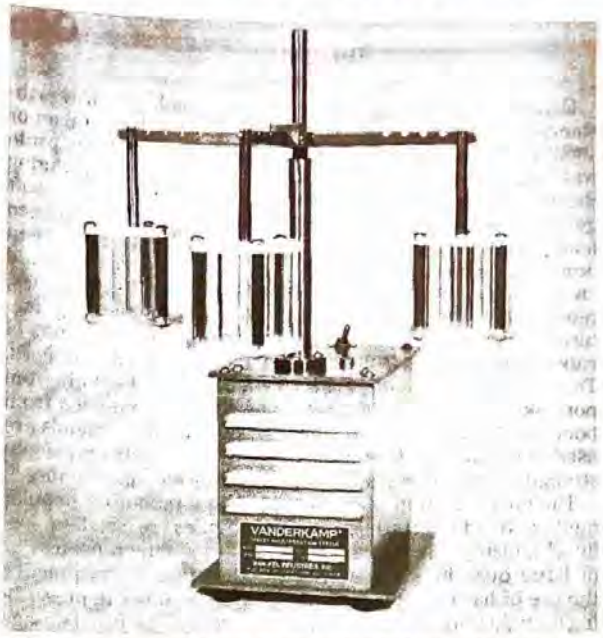


Fig 38. Vanderkamp tablet disintegration tester (courtesy, VanKel).

Validation

In this era of increasing regulatory control of the pharmaceutical industry, manufacturing procedures cannot be discussed without the mention of some process validation activity. By way of documentation, product testing and, perhaps, in-process testing as well, the manufacturer can demonstrate that his formula and process perform in the manner expected and that it does so reproducibly.

Although the justification for requiring validation is found in the regulations relating to "Current Good Manufacturing Practices for Finished Pharmaceuticals" as well as other sources, there is still much room for interpretation and the process varies from one company to another. General areas of agreement appear to be that

The validation activity must begin in R&D and continue through product introduction.

Documentation is the key.

In general, three batches represent an adequate sample for validation.

The FDA has rejected historical data or "retrospective validation." They require that new products be validated from beginning to end, a process called "prospective validation."

Capsules

Capsules are solid dosage forms in which the drug substance is enclosed in either a hard or soft, soluble container or shell of a suitable form of gelatin. The soft gelatin capsule was invented by Mothes, a French pharmacist in 1833. During the following year DuBlanc obtained a patent for his soft gelatin capsules. In 1848 Murdock patented the two-piece hard gelatin capsule. Although development work has been done on the preparation of capsules from methylcellulose and calcium alginate, gelatin, because of its unique properties, remains the primary composition material for the manufacture of capsules. The gelatin used in the manufacture of capsules is obtained from collagenous material by hydrolysis. There are two types of gelatin, Type A, derived mainly from pork skins by acid processing, and Type B, obtained from bones and animal skins by alkaline processing. Blends are used to obtain gelatin solutions with the viscosity and bloom strength characteristics desirable for capsule manufacture.[50]

The encapsulation of medicinal agents remains a popular method for administering drugs. Capsules are tasteless, easily administered and easily filled either extemporaneously or in large quantities commercially. In prescription practice the use of hard gelatin capsules permits a choice in prescribing a single drug or a combination of drugs at the exact dosage level considered best for the individual patient. This flexibility is an advantage over tablets. Some patients find it easier to swallow capsules than tablets, therefore preferring to take this form when possible. This preference has prompted pharmaceutical manufacturers to market the product in capsule form even though the product already has been produced in tablet form. While the industry prepares approximately 75% of its solid dosage forms as compressed tablets, 23% as hard gelatin capsules and 2% as soft elastic capsules, market surveys have indicated a consumer preference of 44.2% for soft elastic capsules, 39.6% for tablets and 19.4% for hard gelatin capsules.[51]

Hard Gelatin Capsules

The hard gelatin capsule, also referred to as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely surrounding the drug formulation. The classic capsule shape is illustrated in Fig 39. These capsules are filled by introducing the powdered material into the longer end or body of the capsule and then slipping on the cap. Hard gelatin capsules are made largely from gelatin, FD&C colorants and sometimes an opacifying agent such as titanium dioxide; the USP permits the gelatin for this purpose to contain 0.15% sulfur dioxide to prevent decomposition during manufacture. Hard gelatin capsules contain 12 to 16% water, but the water content can vary depending on the storage conditions. When the humidity is low, the capsules become brittle; if stored at high humidities, the capsules become flaccid and lose their shape. Storage in high temperature areas also can affect the quality of hard gelatin capsules. Gelatin capsules do not protect hygroscopic materials from atmospheric water vapor as moisture can diffuse through the gelatin wall.

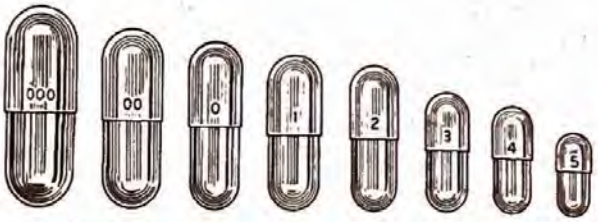


Fig 39. Hard gelatin capsules showing relatives sizes (courtesy, Parke-Davis).

Companies having equipment for preparing empty hard gelatin capsules include *Lilly*, *Parke-Davis*, *Scherer* and *SmithKline*. The latter's production is mainly for its own use; the others are suppliers to the industry. With this equipment stainless-steel pins, set in plates, are dipped into a gelatin solution, which must be maintained at a uniform temperature and an exact degree of fluidity. If the gelatin solution varies in viscosity, it correspondingly will decrease or increase the thickness of the capsule wall. This is important since a slight variation is sufficient to make either a loose or a tight joint. When the pins have been withdrawn from the gelatin solution, they are rotated while being dried in kilns through which a strong blast of filtered air with controlled humidity is forced. Each capsule is stripped, trimmed to uniform length and joined, the entire process being mechanical. Capsule-making equipment is illustrated in Figs 40 and 41. These show the stainless-steel pins being dipped into the gelatin solutions and then being rotated through the drying kiln.

Capsules are supplied in a variety of sizes. The hard, empty capsules (Fig 39) are numbered from 000, the largest size which can be swallowed, to 5, which is the smallest. Larger sizes are available for use in veterinary medicine. The approximate capacity for capsules from 000 to 5 ranges from 600 to 30 mg, although this will vary because of the different densities of powdered drug materials.

Commercially filled capsules have the conventional oblong shape illustrated with the exception of capsule products by *Lilly* and *SmithKline*, which are of distinctive shape. For Lilly products, capsules are used in which the end of the body is tapered to give the capsule a bullet-like shape; products encapsulated in this form are called *Pulvules*. The *SmithKline* capsules differ in that both the ends of the cap and body are angular, rather than round.

After hard gelatin capsules are filled and the cap applied, there are a number of methods used to assure that the capsules will not come apart if subjected to vibration or rough handling, as in high-speed counting and packaging equipment. The capsules can be spot-welded by means of a heated metal pin pressed against the cap, fusing it to the body, or they may be banded with molten gelatin laid around the joint in a strip and dried. Colored gelatin bands around capsules have been used for many years as a trademark by *Parke-Davis* for their line of capsule products, *Kapseals*. Another approach is used in the *Snap-Fit* and *Coni-Snap* capsules. A pair of matched locking rings are formed into the cap and body portions of the capsule. Prior to filling, these capsules are slightly longer than regular capsules of the same size. When

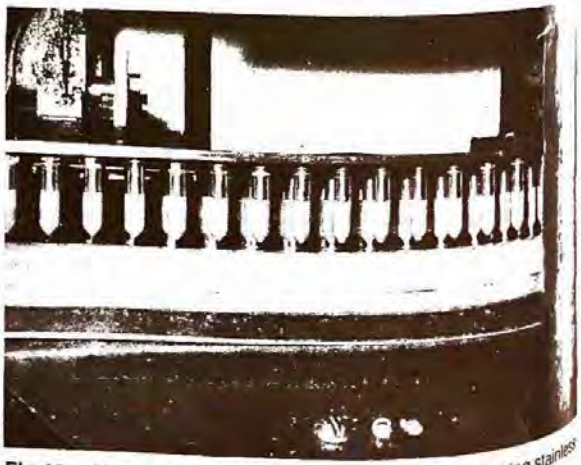


Fig 40. Manufacture of hard gelatin capsules by dipping stainless steel pins into gelatin solutions (courtesy, Lilly).

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

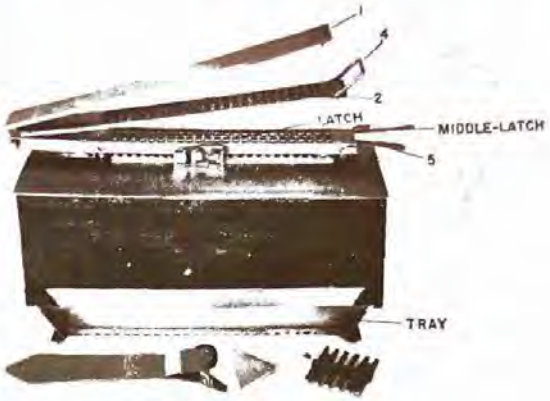


Fig 42. Hand-operated capsule machine (courtesy, Chemi-Pharm).

the locking rings are engaged after filling, their length is equivalent to that of the conventional capsule.

Following several tampering incidents, many pharmaceutical companies now use any number of locking and sealing technologies in order safely to manufacture and distribute these very useful dosage forms. Unfortunately, tamper-resistant packaging has become standard for capsule products.

It is usually necessary for the pharmacist to determine the size of the capsule needed for a given prescription through experimentation. The experienced pharmacist, having calculated the weight of material to be held by a single capsule, often will select the correct size immediately. If the material is powdered, the base of the capsule is filled and the top is replaced. If the material in the capsule proves to be too heavy after weighing, a smaller size must be taken and the test repeated. If the filled capsule is light, it is possible that more can be forced into it by increasing the pressure or, if necessary, some of the material may be placed in the cap. This is not desirable as it tends to decrease the accuracy of subdivision and it is much better to select another size, the base of which will hold exactly the correct quantity. In prescription filling it is wise to check the weight of each filled capsule.

In addition to the transparent, colorless, hard gelatin capsule, capsules are also available in various transparent colors such as pink, green, reddish-brown, blue, yellow and black. If they are used, it is important to note the color as well as the capsule size on the prescription so that in the case of renewal the refilled prescription will duplicate the original. Colored capsules have been used chiefly by manufacturers to give a specialty product a distinctive appearance. Titanium dioxide is added to the gelatin to form white capsules, or to make an opaque, colored capsule. In addition to color contrasts, many commercial products in capsules are given further identification by markings which may be the company's name, a symbol on the outer shell of the capsule or by banding. Some manufacturers mark capsules with special numbers based on a coded system to permit exact identification by the pharmacist or physician.

Extemporaneous Filling Methods

When filling capsules on prescription, the usual procedure is to mix the ingredients by trituration, reducing them to a fine and uniform powder. The principles and methods for the uniform distribution of an active medicinal agent in a powder mixture are discussed in Chapter 91. Granular powders do not pack readily in capsules and crystalline materials, especially those which consist of a mass of filament-like crystals such as the quinine salts, are not fitted easily into capsules unless powdered. Eutectic mixtures that tend to liquefy may be dispensed in capsules if a suitable absorbent such as magnesium carbonate is used. Potent drugs given in small doses usually are mixed with an inert diluent such as lactose before filling into capsules. When incompatible materials are prescribed together, it is sometimes possible to place one in a smaller capsule and then enclose it with the second drug in a larger capsule.

Usually, the powder is placed on paper and flattened with a spatula so that the layer of powder is not greater than about ⅓ the length of the capsule which is being filled. This helps to keep both the hands and capsules clean. The cap is removed from the selected capsule and held in the left hand; the body is pressed repeatedly into the powder until it is filled. The cap is replaced and the capsule is weighed. In filling the capsule the spatula is helpful in pushing the last quantity of the material into the capsule. If each capsule has not been weighed, there is likely to be an excess or a shortage of material when the specified number of capsules have been packed. This condition is adjusted before dispensing the prescription.

A number of manual filling machines and automatic capsule machines are available for increasing the speed of the capsule-filling operation. Figure 42 illustrates a capsule-filling machine which was known formerly as the Sharp & Dohme machine. This equipment is now available through *ChemiPharm*. Many community pharmacists find this a useful piece of apparatus and some pharmaceutical manufacturers use it for small-scale production of specialty items. The machine fills 24 capsules at a time with the possible production of 2000 per day. Entire capsules are placed in the machine by hand; the lower plate carries a clamp which holds the capsule bases and makes it possible to remove and replace the caps mechanically. The plate holding the capsule bases is perforated for three sizes of capsules. The powder is packed in the bases; the degree of accuracy depends on the selection of capsule size and the amount of pressure applied in packing. The hand-operated machine (Model 300, *ChemiPharm*) illustrated in Fig 43 has a production capacity of 2000 capsules per hour. The machine is made for a single capsule size and cannot be changed over for other sizes. A different machine is required for any additional capsule size. Its principle of operation is similar to that of the Sharp & Dohme machine.

Machine Filling Methods

Large-scale filling equipment for capsules operates on the same principle as the manual machines described above, namely the filling of the base of the capsule. Compared with tablets, powders for filling into hard gelatin capsules require the minimum of formulation efforts. The powders usually contain diluents such as lactose, mannitol, calcium carbonate

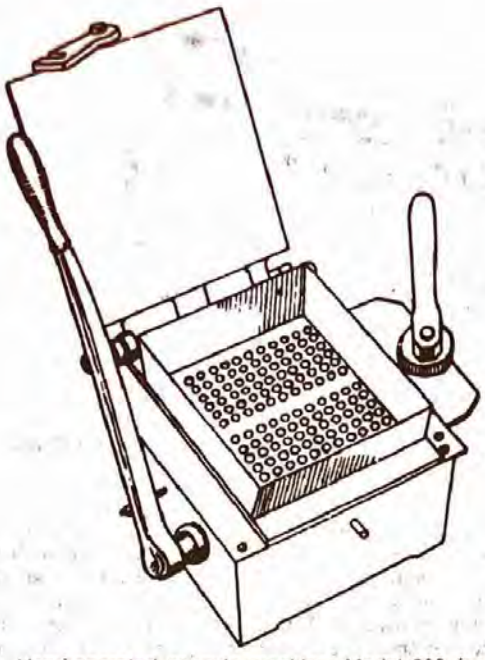


Fig 43. Hand-operated capsule machine, Model 300 (courtesy, ChemiPharm).

or magnesium carbonate. Since the flow of material is of great importance in the rapid and accurate filling of the capsule bodies, lubricants such as the stearates also are used frequently.

Because of the absence of numerous additives and manufacturing processing, the capsule form is used frequently to administer new drug substances for evaluation in initial clinical trials. However, it is now realized that the additives present in the capsule formulation, like the compressed tablet, can influence the release of the drug substance from the capsule. Tablets and capsules of a combination product containing triamterene and hydrochlorothiazide in a 2:1 ratio were compared clinically. The tablet caused approximately twice as much excretion of hydrochlorothiazide and 3 times as much triamterene as the capsule.[52]

Most equipment operates on the principle whereby the base of the capsule is filled and the excess is scraped off. Therefore, the active ingredient is mixed with sufficient volume of a diluent, usually lactose or mannitol, which will give the desired amount of the drug in the capsule when the base is filled with the powder mixture. The manner of operation of the machine can influence the volume of the powder which will be filled into the base of the capsule; therefore, the weights of the capsules must be checked routinely as they are filled. See Table 5.

Semiautomatic capsule-filling machines manufactured by *Parke-Davis* and *Lilly* are illustrated in Figs 44 and 45. The Type 8 capsule-filling machine performs mechanically under the same principle as the hand filling of capsules. This includes separation of the cap from the body, filling the body half and rejoining the cap and body halves.

Empty capsules are taken from the bottom of the capsule hopper into the magazine. The magazine gauge releases one capsule from each tube at the bottom of each stroke of the machine. Leaving the magazine, the capsules drop onto the tracks of the raceway and are pushed forward to the rectifying area with a push blade. The rectifier block descends, turning the capsules in each track, cap up, and drops them into each row of holes in the capsule-holding ring assembly.

As the capsules fall into the holding ring, the cap half has a seat on the counter bore in each hole for the top ring. The

Table 5—Capsule Fill Chart

Capsule Fill Weights (mg) Based on Size and Density

Powder density (g/mL)	Capsule volume (mL) 0.95	0.78	0.68	0.54	0.5	0.37	0.3	0.25	0.21	0.1
	Capsule size OO	Oel	O	1el	1	2	3	4el	4	5
0.3	285	234	204	162	150	111	90	75	63	3
0.4	380	312	272	216	200	148	120	100	84	5
0.5	475	390	340	270	250	185	150	125	105	6
0.6	570	468	408	324	300	222	180	150	126	7
0.7	665	546	476	378	350	259	210	175	147	8
0.8	760	624	544	432	400	296	240	200	168	9
0.9	855	702	612	486	450	333	270	225	189	10
1.0	950	780	680	540	500	370	300	250	210	12
1.1	1045	858	748	594	550	407	330	275	231	13
1.2	1140	936	816	648	600	444	360	300	252	14
1.3	1235	1014	884	702	650	481	390	325	273	15
1.4	1330	1092	952	756	700	518	420	350	294	16
1.5	1425	1170	1020	810	750	555	450	375	315	17

body half is pulled by vacuum down into the bottom ring. When all rows in the ring assembly are full, the top ring, filled with caps only, is removed and set aside for later assembly. The body halves now are located in the bottom ring, ready for filling.

The ring holding the body halves is rotated at one of eight speeds on the rotary table. The drug hopper is swung over the rotating ring and the auger forces drug powder into the open body cavities. When the ring has made a complete revolution and the body halves have been filled, the hopper is swung aside. The cap-holding ring is placed over the body-holding ring and the assembly is ready for joining. The capsule-holding ring assembly is placed on the joiner and the joiner plate is swung down into position to hold the capsules in the ring. The peg ring pins are entered in the holes of the body holding ring and tapped in place by the air cylinder pushing the body halves back into the cap halves.

The holding-ring assembly is now pushed by hand back onto the peg ring away from the joiner plate, thus pushing the capsules out of the holding-ring assembly. The joined capsules then fall through the joiner chute into the capsule re-

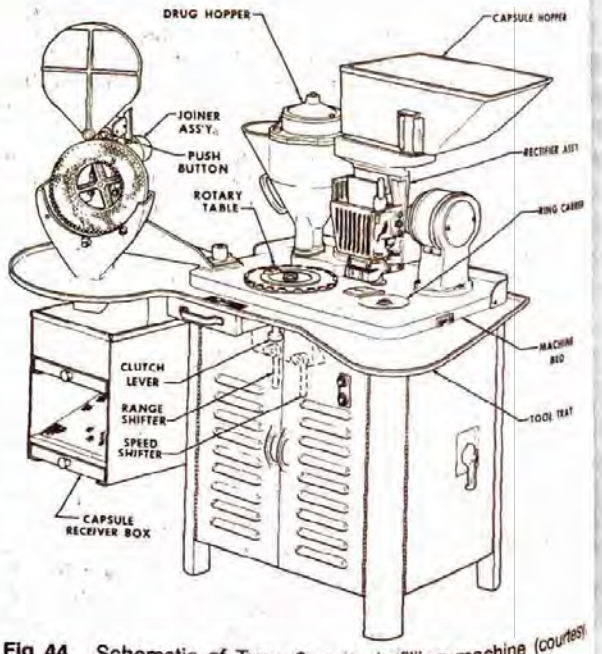


Fig 44. Schematic of Type 8 capsule-filling machine (courtesy Parke-Davis).

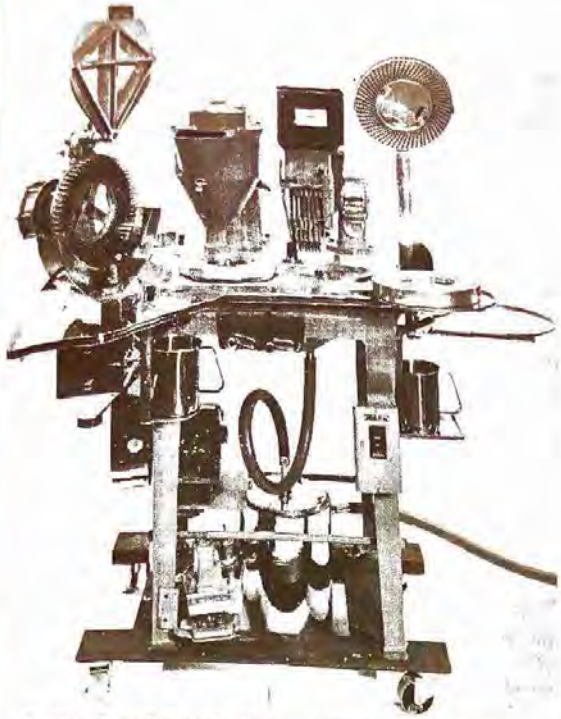


Fig 45. Type 8 capsule-filling machine (courtesy, Lilly).

ceiver box. The capsule receiver box screens the excess powder from the capsules and delivers them to any convenient container.

Many companies use the Type 8 capsule-filling equipment for small-scale manufacture and clinical supplies for investigational use because of its ease of operation, low cost and extreme flexibility. A Type 8 capsule filling machine will produce approximately 200,000 capsules per day. This, of course, depends upon the operator and the type of material being filled. For this machine, a mathematical model has been developed that describes the effect of selected physical powder properties, as well as mechanical operating conditions on the capsule filling operation. While the Type 8 capsule-filling machine has been in existence for many years, recent modifications have been made to this machine to improve the capsule-filling operations.

There are several pieces of equipment available that are classified as automatic capsule-filling machines. These are automatic in the sense that one operator can handle more than one machine. In this category are the Italian-made Zanasi (*United Machinery*) and MG-2 (*Supermatic*) models plus the West German-made Hoefliger & Karg models (*Bosch*).

Automatic capsule machines are capable of filling either powder or granulated products into hard gelatin capsules. With accessory equipment these machines also can fill pellets or place a tablet into the capsule with the powder or pellets. The capsules are fed at random into a large hopper. They are oriented as required and transferred into holders where the two halves are separated by suction. The top-half and bottom-half of the capsules are each in a separate holder, which at this stage take diverting directions.

A set of filling heads collect the product from the hopper, compresses it into a soft slug and inserts this into the bottom half of the capsule. After filling, each top-half is returned to the corresponding bottom-half. The filled capsules are ejected and an air blast at this point separates possible empty capsules from the filled. The machines can be equipped to handle all sizes of capsules. Depending upon the make and model, speeds from 9000 to 150,000 units per hour can be obtained (see Figs 46–48).

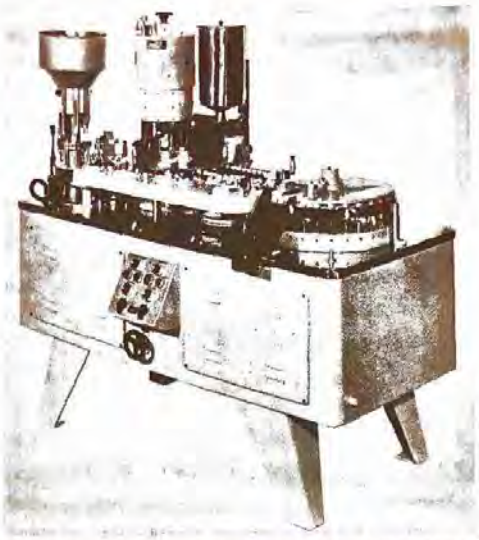


Fig 46. MG-2, automatic capsule-filling machine (courtesy, Supermatic).

All capsules, whether they have been filled by hand or by machine, will require cleaning. Small quantities of capsules may be wiped individually with cloth. Larger quantities are rotated or shaken with crystalline sodium chloride. The capsules then are rolled on a cloth-covered surface.

Uniformity of Dosage Units

The uniformity of dosage forms can be demonstrated by either of two methods, weight variation or content uniformity. Weight variation may be applied where the product is a liquid-filled soft elastic capsule or where the hard gelatin capsule contains 50 mg or more of a single active ingredient comprising 50% or more, by weight, of the dosage form. See the official compendia for details.

Disintegration tests usually are not required for capsules unless they have been treated to resist solution in gastric fluid (enteric-coated). In this case they must meet the requirements for disintegration of enteric-coated tablets. For certain capsule dosage forms a dissolution requirement is part of

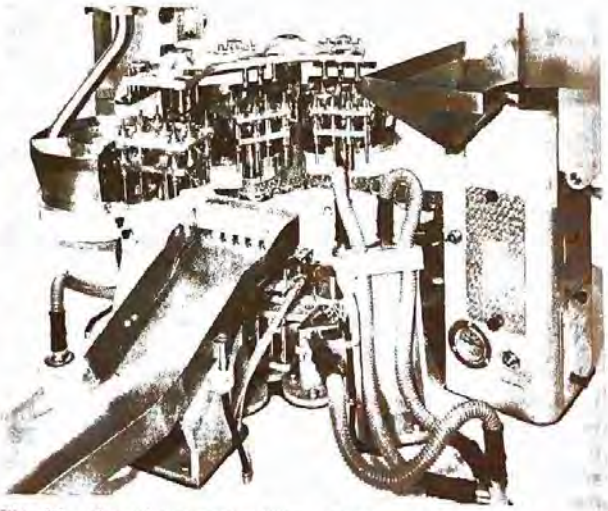


Fig 47. Zanasi automatic filling machine, Model AZ-60. The set of filling heads shown at the left collects the powder from the hopper, compresses it into a soft slug and inserts it into the bottom half of the capsule (courtesy, United Machinery).

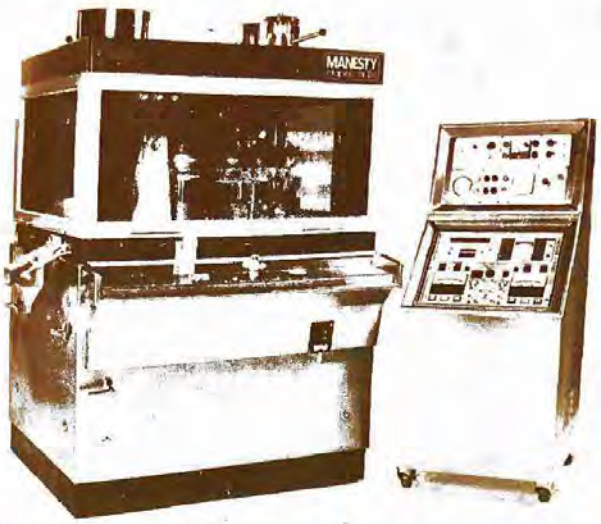


Fig 48. Hoefliger & Karg automatic capsule-filling machine, Model GFK 1200 (courtesy, Amaco).

the monograph. Procedures used are similar to those employed in the case of compressed tablets. (See Chapter 34).

Soft Elastic Capsules

The soft elastic capsule (SEC) is a soft, globular, gelatin shell somewhat thicker than that of hard gelatin capsules. The gelation is plasticized by the addition of glycerin, sorbitol or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of fungi. Commonly used preservatives are methyl- and propylparabens and sorbic acid. Where the suspending vehicle or solvent can be an oil, soft gelatin capsules provide a convenient and highly acceptable dosage form. Large-scale production methods generally are required for the preparation and filling of soft gelatin capsules.

Formerly, empty soft gelatin capsules were available to the pharmacist for the extemporaneous compounding of solutions or suspensions in oils. Commercially filled soft gelatin capsules come in a wide choice of sizes and shapes; they may be round, oval, oblong, tube or suppository-shaped. Some sugar-coated tablets are quite similar in appearance to soft gelatin capsules. The essential differences are that the soft gelatin capsule has a seam at the point of closure of the two halves, and the contents can be liquid, paste or powder. The sugar-coated tablet will not have a seam but will have a compressed core.

Oral SEC dosage forms generally are made so that the heat seam of the gelatin shell opens to release its liquid medication into the stomach less than 5 minutes after ingestion. Its use is being studied for those drugs poorly soluble in water having bioavailability problems. When used as suppositories, it is the moisture present in the body cavity that causes the capsule to come apart at its heat-sealed seam and to release its contents.

Plate Process

In this method a set of molds is used. A warm sheet of prepared gelatin is laid over the lower plate and the liquid is poured on it. A second sheet of gelatin is carefully put in place and this is followed by the top plate of the mold. The set is placed under the press where pressure is applied to form the capsules which are washed off with a volatile solvent to remove any traces of oil from the exterior. This process has been adapted and is used for encapsulation by *Upjohn*. The sheets of gelatin may have the same color or different colors.

Fig 49. Rotary-die elastic capsule filler.

Rotary-Die Process

In 1933 the rotary-die process for elastic capsules was perfected by Robert P Scherer.[53] This process made it possible to improve the standards of accuracy and uniformity of elastic gelatin capsules and globules.

The rotary-die machine is a self-contained unit capable of continuously and automatically producing finished capsules from a supply of gelatin mass and filling material which may be any liquid, semiliquid or paste that will not dissolve gelatin. Two continuous gelatin ribbons, which the machine forms, are brought into convergence between a pair of revolving dies and an injection wedge. Accurate filling under pressure and sealing of the capsule wall occur as dual and coincident operations; each is delicately timed against the other. Sealing also severs the completed capsule from the net. The principle of operation is shown in Fig 49. See also Fig 50.

By this process the content of each capsule is measured individually by a single stroke of a pump so accurately constructed that plunger travel of 0.025 inch will deliver 1 m (apoth). The Scherer machine contains banks of pumps so arranged that many capsules may be formed and filled simultaneously. All pumps are engineered to extremely small mechanical tolerances and to an extremely high degree of precision and similarity. All operations are controlled on a weight basis by actual periodic checks with a group of analytical balances. Individual net-fill weights of capsules resulting

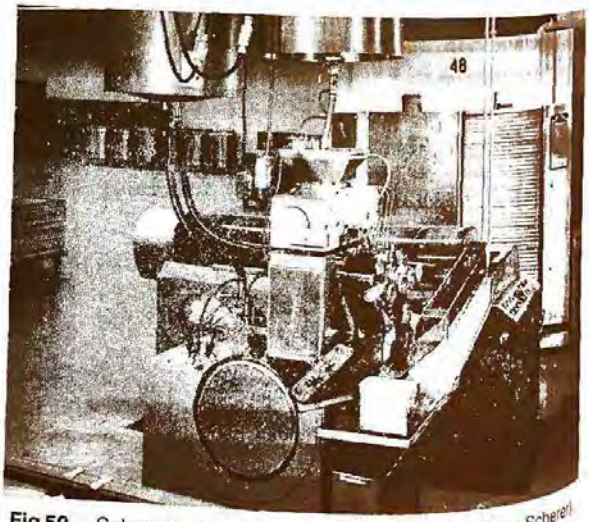


Fig 50. Scherer soft elastic capsule machine (courtesy, Scherer)

from large-scale production vary no more than ±1 to 3% from theory depending upon the materials used.

The rotary-die process makes it possible to encapsulate heavy materials such as ointments and pastes. In this manner solids can be milled with a vehicle and filled into capsules. Where it is desirable to have a high degree of accuracy and a hermetically sealed product, this form of enclosure is suited ideally.

The modern and well-equipped capsule plant is completely air conditioned, a practical necessity for fine capsule production. Its facilities and operations include the availability of carbon dioxide at every exposed point of operation for the protection of oxidizable substances before encapsulation. Special ingredients also have been used in the capsule shell to exclude light wavelengths which are destructive to certain drugs.

Norton Capsule Machine

This machine produces capsules completely automatically by leading two films of gelatin between a set of vertical dies. These dies as they close, open and close are, in effect, a continual vertical plate forming row after row of pockets across the gelatin film. These are filled with medicament and, as they progress through the dies, are sealed, shaped and cut out of the film as capsules which drop into a cooled solvent bath.

Accogel Capsule Machine

Another means of soft gelatin encapsulation uses the Accogel machine and process which were developed in the *Lederle*. The Accogel, or Stern machine, uses a system of rotary dies but is unique in that it is the only machine that successfully can fill dry powder into a soft gelatin capsule. The machine is available to the entire pharmaceutical industry by a lease arrangement and is used in many countries of the world. It is extremely versatile, not only producing capsules with dry powder but also encapsulating liquids and combinations of liquids and powders. By means of an attachment, slugs or compressed tablets may be enclosed in a gelatin film. The capsules can be made in a variety of colors, shapes and sizes.

Microencapsulation

As a technology, microencapsulation is placed in the section on capsules only because of the relationship in terminology to mechanical encapsulation described above. The topic also could have been included in a discussion of coating procedures. Essentially, microencapsulation is a process or technique by which thin coatings can be applied reproducibly to small particles of solids, droplets of liquids or dispersions, thus forming microcapsules. It can be differentiated readily from other coating methods in the size of the particles involved; these range from several tenths of a μm to 5000 μm in size.

A number of microencapsulation processes have been disclosed in the literature.[64] Some are based on chemical processes and involve a chemical or phase change; others are mechanical and require special equipment to produce the physical change in the systems required.

A number of coating materials have been used successfully; examples of these include gelatin, polyvinyl alcohol, ethylcellulose, cellulose acetate phthalate and styrene maleic anhydride. The film thickness can be varied considerably depending on the surface area of the material to be coated and other physical characteristics of the system. The microcapsules may consist of a single particle or clusters of particles. After isolation from the liquid manufacturing vehicle and drying, the material appears as a free-flowing powder. The powder is suitable for formulation as compressed tablets, hard gelatin capsules, suspensions and other dosage forms.

The process provides answers for problems such as masking the taste of bitter drugs, a means of formulating prolonged action dosage forms, a means of separating incompatible materials, a method of protecting chemicals against moisture or oxidation and a means of modifying a material's physical characteristics for ease of handling in formulation and manufacture.

Among the processes applied to pharmaceutical problems is that developed by the National Cash Register Co (NCR). The NCR process is a chemical operation based on phase separation or coacervation techniques. In colloidal chemistry, coacervation refers to the separation of a liquid precipitate, or phase, when solutions of two hydrophilic colloids are mixed under suitable conditions.

The NCR process, using phase separation or coacervation techniques, consists of three steps:

1. Formation of three immiscible phases: a liquid manufacturing phase, a core material phase and a coating material phase.
2. Deposition of the liquid polymer coating on the core material.
3. Rigidizing the coating, usually by thermal, cross-linking or desolvation techniques, to form a microcapsule.

In Step 2, the deposition of the liquid polymer around the core material occurs only if the polymer is absorbed at the interface formed between the core material and the liquid vehicle phase. In many cases physical or chemical changes in the coating polymer solution can be induced so that phase separation (coacervation) of the polymer will occur. Droplets of concentrated polymer solution will form and coalesce to yield a two-phase liquid–liquid system. In cases where the coating material is an immiscible polymer or insoluble liquid polymer, it may be added directly. Also monomers can be dissolved in the liquid vehicle phase and, subsequently, polymerized at the interface.

Equipment required for microencapsulation by this method is relatively simple; it consists mainly of jacketed tanks with variable speed agitators. Figure 51 shows a typical flow diagram of a production installation.

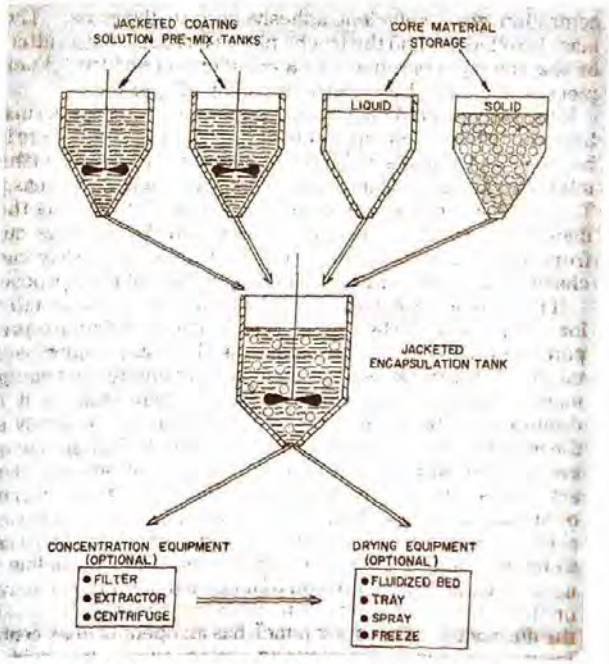


Fig 51. Production installation for the microencapsulation process (courtesy, NCR).

Pills

Pills are small, round solid dosage forms containing a medicinal agent and are intended for oral administration. Pills were formerly the most extensively used oral dosage form, but they have been replaced largely by compressed tablets and capsules. Substances which are bitter or unpleasant to the taste, if not corrosive or deliquescent, can be administered in this form if the dose is not too large.

Formerly, pills were made extemporaneously by the community pharmacist whose skill at pill-making became an art. However, the few pills which are now used in pharmacy are prepared on a large scale with mechanical equipment. The pill formulas of the NF were introduced largely for the purpose of establishing standards of strength for the well-known and currently used pills. Hexylresorcinol Pills consist of hexylresorcinol crystals covered with a rupture-resistant coating that is dispersible in the digestive tract. It should be noted that the official hexylresorcinol pills are prepared not by traditional methods but by a patented process, the gelatin coating being sufficiently tough that it can not be broken readily, even when chewed. Therefore, the general method for the preparation of pills does not apply to hexylresorcinol pills.

Previous editions of this text should be consulted for methods of pill preparation.

Troches

These forms of oral medication, also known as *lozenges* or *pastilles*, are discoid-shaped solids containing the medicinal agent in a suitably flavored base. The base may be a hard sugar candy, glycerinated gelatin or the combination of sugar with sufficient mucilage to give it form. Troches are placed in the mouth where they slowly dissolve, liberating the active ingredient. The drug involved can be an antiseptic, local anesthetic, antibiotic, antihistaminic, antitussive, analgesic or a decongestant.

Formerly, troches were prepared extemporaneously by the pharmacist. The mass is formed by adding water slowly to a mixture of the powdered drug, powdered sugar and a gum until a pliable mass is formed. Powdered acacia in 7% concentration gives sufficient adhesiveness to the mass. The mass is rolled out and the troche pieces cut out using a cutter, or else the mass is rolled into a cylinder and divided. Each piece is shaped and allowed to dry before dispensing.

If the active ingredient is heat-stable, it may be prepared in a hard candy base. Syrup is concentrated to the point where it becomes a pliable mass, the active ingredient is added and the mixture is kneaded while warm to form a homogeneous mass. The mass is worked gradually into a pipe form having the diameter desired for the candy piece and the lozenges cut from the pipe and allowed to cool. This is an entirely mechanical operation with equipment designed for this purpose.

If the active ingredient is heat-labile, it may be made into a lozenge preparation by compression. The granulation is prepared in a manner similar to that used for any compressed tablet. The lozenge is made using heavy compression equipment to give a tablet which is harder than usual as it is desirable for the troche to dissolve or disintegrate slowly in the mouth. In the formulation of the lozenge the ingredients are chosen which will promote its slow-dissolving characteristics. Compression is gaining in popularity as a means of making troches and candy pieces because of the increased speeds of compression equipment. In cases where holes are to be placed in troches or candy pieces, core-rod tooling is used (see Fig 52). Core-rod tooling includes a rod centered on the lower punch around which the troche is compressed in the die cavity. The upper punch has an opening in its center for the core rod to enter during compression. It is evident that maximum accuracy is needed to provide alignment as the narrow punches are inserted into the die.

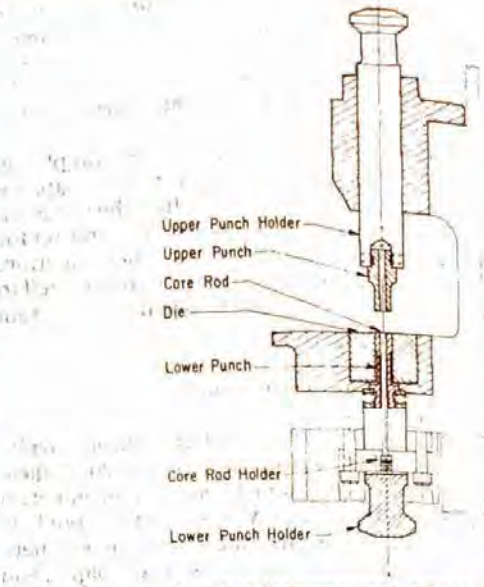


Fig 52. Core-rod tooling for compressing troches or candy pieces with hole in center (courtesy, Vector/Colton).

Cachets

Related to capsules, inasmuch as they provide an edible container for the oral administration of solid drugs, cachets formerly were used in pharmacy. They varied in size from ⅛ to ⅛ in in diameter and consisted of two concave pieces of wafer made of flour and water. After one section was filled with the prescribed quantity of the medicinal agent, they were sealed tightly by moistening the margins and pressing them firmly together. When moistened with water, their character was changed entirely; they became soft, elastic and slippery. Hence, they could be swallowed easily by floating them in water.

Pellets

The term pellet is now applied to small, sterile cylinders about 3.2 mm in diameter by 8 mm in length, which are formed by compression from medicated masses.[55] Whenever prolonged and continuous absorption of testosterone, estradiol or desoxycorticosterone is desired, pellets of these potent hormones may be used by implantation.

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CHAPTER 93

Coating of Pharmaceutical Dosage Forms

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Any introduction to tablet coating must be prefaced by an important question—"Why coat tablets?"—since in many instances, the coating is being applied to a dosage form that already is functionally complete. In attempting to answer this question, if one examines the market, it will become apparent that a significant proportion of pharmaceutical solid dosage forms are coated. The reasons for this range from the esthetic to a desire to control the bioavailability of the drug, and include:

1. Protecting the drug from its surrounding environment (particularly air, moisture and light) with a view to improving stability.
2. Masking of unpleasant taste and odor.
3. Increasing the ease by means of which the product can be ingested by the patient.
4. Improving product identity, from the manufacturing plant, through intermediaries and to the patient.
5. Facilitating handling, particularly in high-speed packaging/filling lines, and automated counters in pharmacies, where the coating minimizes cross-contamination due to dust elimination.
6. Improving product appearance, particularly where there are noticeable visible differences in tablet core ingredients from batch to batch.
7. Reducing the risk of interaction between incompatible components. This would be achieved by using coated forms of one or more of the offending ingredients (particularly active compounds).
8. Improving product mechanical integrity, since coated products generally are more resistant to mishandling (abrasion, attrition, etc).
9. Modifying drug release, as in enteric-coated, repeat-action and sustained-release products.

Evolution of the Coating Process—Tablet coating is perhaps one of the oldest pharmaceutical processes still in existence. Although a great deal has been written about the materials and methods used, the coating process is still often recognized to be more of an art than a science, a factor which may be responsible for many of the problems that can exist. Historically, the literature cites Rhazes (850–932 AD) as being one of the earliest "tablet coaters," having used the mucilage of psyllium seeds to coat pills that had an offending taste. Subsequently, Avicenna[1] was reported to have used gold and silver for pill coating. Since then, there have been many references to the different materials used in "tablet coating." White[2] mentioned the use of finely divided talc in what was at one time popularly known as "pearl coating," while Kremers and Urdang[3] described the introduction of the gelatin coating of pills by Garot in 1838.

An interesting reference[4] reports the use of waxes to coat poison tablets. These waxes, being insoluble in all parts of the gastrointestinal tract, were intended to prevent accidental poisoning (the contents could be utilized by breaking the tablet prior to use).

While earlier coated products were produced by individuals working in pharmacies, particularly when extemporaneous compounding was the order of the day, that responsibility now has been assumed by the pharmaceutical industry. The earliest attempts to apply coatings to pills yielded variable results and usually required the handling of single pills. Such pills would have been mounted on a needle or held with a pair of forceps and literally dipped into the coating fluid, a procedure which would have to be repeated more than once to ensure that the pill was coated completely. Subsequently, the pills were held at the end of a suction tube, dipped and then the process repeated for the other side of the pill. Not surprisingly, these techniques often failed to produce a uniformly coated product.[5]

Initially, the first sugar-coated pills seen in the US were imported from France about 1842;[5] while Warner, a Philadelphia pharmacist, became among the first indigenous manufacturers in 1856.[6]

Pharmaceutical pan-coating processes are based on those used in the candy industry, where techniques were highly evolved, even in the Middle Ages. Today, while most coating pans are fabricated from stainless steel, early pans were made from copper, because drying was effected by means of an externally applied heat source. Current thinking, even with conventional pans, is to dry the coated tablets with a supply of heated air, and remove the moisture and dust-laden air from the vicinity of the pan by means of an air-extraction system.

Pan-coating processes underwent little further change until the late 1940s and early 1950s, with the conventional pan being the mainstay of all coating operations up to that time. However, in the last 20 or 30 years there have been some significant advances made in coating-process technology, mainly as a result of a steady evolution in pan design and its associated ancillary equipment.

Interestingly, in the early years of this development, an entirely new form of technology evolved, that of film coating. Recognizing the deficiencies of the sugar-coating process, advocates of film coating were achieving success by using coating systems involving highly volatile organic solvents. These circumvented the problems associated with the inefficiency in the drying capabilities of conventional equipment and enabled production quotas to be met with significant reductions in processing times and materials used. The disadvantage of this approach, however, always has been associated with the solvent systems used, which often employed flammable and toxic materials.

The advances that occurred with equipment design, having begun by the development of the Wurster[7] process and continued by the evolution of side-vented pans, have resulted in the gradual emergence of coating processes where drying efficiency can be maximized. Thus, film coating began as a process using inefficient drying equipment, relying on highly volatile coating formulations for success, and evolved into one in which the processing equipment is a major factor in ensuring that rapid drying occurs. Improved drying capabilities have permitted increased use of aqueous film-coating formulations.

Advances in equipment design also have benefited the sugar-coating process, where, because of Current Good Manufacturing Practices (CGMP) and to maintain product uniformity and performance, the trend has been toward using fully automated processes. Nonetheless, film coating tends to dominate as the process of choice for tablet coating.

Pharmaceutical Coating Processes

Basically, there are four major techniques for applying coatings to pharmaceutical solid dosage forms: (1) sugar coat-

ing, (2) film coating, (3) microencapsulation and (4) compression coating.

Although it could be argued that the use of mucilage of psyllium seed, gelatin, etc, as already discussed, was an early form of film coating, *sugar coating* is regarded as the oldest method for tablet coating, and involves the deposition from aqueous solution of coatings based predominantly on sucrose as a raw material. The large quantities of coating material that are applied and the inherent skill often required of the operators combine to result in a long and tedious process.

Film coating, the deposition of a thin polymeric film onto the dosage form from solutions that were initially organic-solvent-based, but which now rely more and more on water as the prime solvent, has proven to be a popular alternative to sugar coating.

Microencapsulation is a modified form of film coating, differing only in the size of the particles to be coated and the methods by which this is accomplished. This process is based on either mechanical methods such as pan coating, air-suspension techniques, multiorifice centrifugal techniques and modified spray-drying techniques, or physicochemical ones involving coacervation-phase separation, where the material to be coated is suspended in a solution of the polymer. Phase separation is facilitated by the addition of a nonsolvent, incompatible polymer, inorganic salts or by altering the temperature of the system.

Compression coating incorporates the use of modified tableting machines which allow the compaction of a dry coating around the tablet core produced on the same machine. The main advantage of this type of coating is that it eliminates the use of any solvent, whether aqueous or organic in nature. However, this process is mechanically complex and has not proven popular as a method for coating tablets.

Sugar Coating of Compressed Tablets

While the term "sugar" is somewhat generic, and lends itself to describing various raw materials, sugar coating relies mainly on the use of sucrose. The main reason for this is that, based on the techniques involved, it is probably the only material which has enabled smooth, high-quality coatings to be produced, that are essentially dry and tack-free at the end of the process.

While the popularity of sugar coating has been on the decline, this process still retains some popularity, and many companies have invested in the complete modernization of the process.

In spite of certain inherent difficulties associated with the sugar-coating process, products which have been expertly sugar coated still remain among the most elegant available.

Since sugar coating is a multistep process, where esthetics of the final coated product is an important goal, it has been, and still is in many companies, highly dependent on the use of skilled manpower. For these reasons, the sugar-coating process is often protracted and tedious. However, processing times have been reduced gradually in the last two decades by the adoption of modern techniques and by the introduction of automation.

The sugar-coating process can be subdivided into six main steps: (1) sealing, (2) subcoating, (3) smoothing, (4) color coating, (5) polishing and (6) printing.

Sealing—The sealing coat is applied directly to the tablet core for the purpose of separating the tablet ingredients (primarily the drug) and water (which is a major constituent of the coating formulation) in order to assure good product stability. A secondary function is to strengthen the tablet core. Sealing coats usually consist of alcoholic solutions (approximately 10–30% solids) of resins such as shellac, zein, cellulose acetate phthalate or polyvinyl acetate phthalate. Historically, shellac has proven to be the most popular material although it can cause impaired bioavailability due to a change in resin properties on storage. A solution to this problem has been to use a shellac-based formulation containing a measured quantity of polyvinylpyrrolidone (PVP).[8]

The quantities of material applied as a sealing coat will depend primarily on the tablet and batch size. However, another important factor is tablet porosity, since highly porous tablets will tend to soak up the first application of solution, thus preventing it from spreading uniformly across the surface of every tablet in the batch. Thus, one or more further applications of resin solution may be necessary to ensure that the tablet cores are sealed effectively.

Since most sealing coats develop a degree of tack (stickiness) at some time during the drying process, it is usual to apply a dusting powder to prevent tablets from sticking together or to the pan. A common material used as a dusting powder is asbestos-free talc. Overzealous use of talc may cause problems, firstly, by imparting a high degree of slip to the tablets, thus preventing them from rolling properly in the pan, and secondly, presenting a surface at the beginning of the subcoating stage which is very difficult to wet, resulting in inadequate subcoat buildup, particularly on the edges. If there is a tendency for either of these problems to occur, one solution is to replace part or all of the talc with some other material such as terra alba, which will form a slightly rougher surface. Use of talc now is being frowned upon because of its potential carcinogenicity.

If an enteric-coated product is required, additional quantities of the seal-coat solution are applied. In this situation, however, it is preferable to use synthetic polymers such as polyvinyl acetate phthalate or cellulose acetate phthalate.

Subcoating—Subcoating is a critical operation in the sugar-coating process that can have a marked effect on ultimate tablet quality. Sugar coating is a process which often leads to a 50 to 100% weight increase, and it is at the subcoating stage that most of the buildup occurs.

Historically, subcoating has been achieved by the application of a gum-based solution to the sealed tablet cores, and once this solution has been distributed uniformly throughout the tablet mass, it is followed by a liberal dusting of powder, which serves to reduce tack and facilitate tablet buildup. This procedure of application of gum solution, spreading, dusting and drying is continued until the requisite buildup has been achieved. Thus, the subcoating is a sandwich of alternate layers of gum and powder. Some examples of binder solutions are shown in Table 1 and those of dusting powder formulations in Table 2.

While this approach has proved to be very effective, particularly where there is difficulty in covering edges. If care is not taken, a "lumpy" subcoat will be the result. Also, if the amount of dusting powder applied is not matched to the binding capacity of the gum solution, not only will the ultimate coating be brittle, but also dust will collect in the back of the pan, a factor which may contribute to excessive roughness.

An alternative approach which has proved popular, particularly when used in conjunction with an automated dosing system, is the application of a suspension subcoat formulation.

Table 1—Binder Solution Formulations for Subcoating

	A, % w/w	B, % w/w
Gelatin	3.3	6.0
Gum acacia (powdered)	8.7	8.0
Sucrose	55.3	45.0
Water	to 100.0	to 100.0

Table 2—Dusting Powder Formulations for Subcoating

	A, % w/w	B, % w/w
Calcium carbonate	40.0	—
Titanium dioxide	5.0	1.0
Talc (asbestos-free)	25.0	61.0
Sucrose (powdered)	28.0	38.0
Gum acacia (powdered)	2.0	—

In such a formulation the powdered materials responsible for coating buildup have been dispersed in a gum-based solution. A typical formulation is shown in Table 3. This approach allows the solids loading to be matched more closely to the binding capacity of the base solution, and often permits the less-experienced coater to achieve satisfactory results.

Smoothing—Depending on how successfully the subcoat was applied, it may be necessary to smooth out the tablet surface further prior to application of the color coating. Smoothing usually can be accomplished by the application of a simple syrup solution (approximately 60 to 70% sugar solids).

Often, the smoothing syrups contain a low percentage of titanium dioxide (1 to 5%) as an opacifier. This can be particularly useful when the subsequent color-coating formulation uses water-soluble dyes as colorants, since it makes the surface under the color coating more reflective, resulting in a brighter, cleaner final color.

Color Coating—This stage often is the most critical in the successful completion of a sugar-coating process, and involves the multiple application of syrup solutions (60 to 70% sugar solids) containing the requisite coloring matter. The types of coloring materials used can be divided into two categories: dyes or pigments. The distinction between the two simply is one of solubility in the coating fluid. Since water-soluble dyes behave entirely differently than water-insoluble pigments, the application procedure used in the color coating of tablets will depend on the type of colorant chosen.

When used by a skilled artisan, water-soluble dyes produce the most elegant of sugar-coated tablets, since it is possible to obtain a cleaner, brighter final color. However, since water-soluble dyes are migratory colorants (that is to say, moisture that is removed from the coating on drying will cause migration of the colorant, resulting in a nonuniform appearance), great care must be exercised in their use, particularly when dark shades are required. This can be achieved by applying small quantities of colored syrup that are just sufficient to wet the surface of every tablet in the batch, and then allowing the tablets to dry slowly. It is essential that each application is allowed to dry thoroughly before subsequent applications are made, otherwise moisture may become trapped in the coating and may cause the tablets to "sweat" on standing.

The final color obtained may result from up to 60 individual applications of colored syrup. This factor, combined with the need to dry each application slowly and thoroughly, results in very long processing times (eg, assuming 50 applications are made which take between 15 and 30 minutes each, the coloring process can extend over a period of up to 25 hours).

Tablet color coating with pigments, as advocated by Tucker *et al*,[9] can present some significant advantages. First of all, since pigment colors are water-insoluble, they present no problems of migration since the colorant remains where it is deposited. In addition, if the pigment is opaque, or is combined with an opacifier such as titanium dioxide, the desired color can be developed much more rapidly, thus resulting in a thinner color coat. Since each color-syrup application now can be dried more rapidly, fewer applications are required and significant reductions can be made in both processing times and costs.

Table 3—Typical Suspension Subcoating Formulation

	% w/w
Distilled water	25.0
Sucrose	40.0
Calcium carbonate	20.0
Talc (asbestos-free)	12.0
Gum acacia (powdered)	2.0
Titanium dioxide	1.0

Although pigment-based color coatings are by no means foolproof, they will permit more abuse than a dye color coating approach, and are more amenable for use by less skilled coaters. Pharmaceutically acceptable pigments can be classified either as inorganic pigments (eg, titanium dioxide, iron oxides) or certified lakes. Certified lakes are produced from water-soluble dyes by means of a process known as "laking," whereby the dye molecule becomes fixed to a suitable insoluble substrate such as aluminum hydroxide.

Certified lakes, particularly when used in conjunction with an opacifier such as titanium dioxide, provide an excellent means of coloring sugar coatings and permit a wide range of shades to be achieved. However, the incorporation of pigments into the syrup solution is not as easy as with water-soluble dyes, since it is necessary to ensure that the pigment is wetted completely and dispersed uniformly. Thus, the use of pigment color concentrates, which are commercially available, is usually beneficial.

Polishing—Sugar-coated tablets need to be polished in order to achieve a final gloss. Polishing is achieved by applying mixtures of waxes (beeswax, carnauba wax, candelilla wax or hard paraffin wax) to the tablets in a polishing pan. Such wax mixtures may be applied as powders or as dispersions in various organic solvents.

Printing—In order to identify sugar-coated tablets (in addition to shape, size and color) often it is necessary to print them, either before or after polishing, using pharmaceutical branding inks, by means of the process of *offset rotogravure*.

Sugar-Coating Problems—Various problems may be encountered during the sugar coating of tablets. It must be remembered that any process in which tablets are kept tumbling constantly can present difficulties if the tablets are not strong enough to withstand the applied stress. Tablets which are too soft, or have a tendency to laminate, may break up and the fragments adhere to the surface of otherwise good tablets.

Sugar-coating pans exhibit inherently poor mixing characteristics. If care is not exercised during the application of the various coating fluids, nonuniform distribution of coating material can occur, resulting in an unacceptable range of sizes of finished tablets within the batch.

Overzealous use of dusting powders, particularly during the subcoating stage, may result in a coating being formed in which the quantity of fillers exceeds the binding capacity of the polymer used in the formulation, creating soft coatings or those with increased tendency to crack.

Irregularities in appearance are not uncommon, and occur either as the result of color migration during drying when water-soluble dyes are used, or of "washing back" when overdosing of colored syrups causes the previously dried coating layers to be redissolved. Rough tablet surfaces will produce a "marbled" appearance during polishing, since wax buildup occurs in the small depressions in the tablet surface.

Film Coating of Solid Dosage Forms

Film coating involves the deposition of a thin, but uniform, film onto the surface of the substrate. Unlike sugar coating, the flexibility afforded in film coating allows additional substrates, other than just compressed tablets, to be considered (eg, powder, granules, nonpareils, capsules). Coatings essentially are applied continuously to a moving bed of material, usually by means of a spray technique, although manual application procedures have been used.

Historically, film coating was introduced in the early 1950s in order to combat the shortcomings of the then predominant sugar-coating process. Film coating has proved successful as a result of the many advantages offered, including:

1. Minimal weight increase (typically 2 to 3% of tablet core weight).
2. Significant reduction in processing times.
3. Increased process efficiency and output.
4. Increased flexibility in formulations.
5. Improved resistance to chipping of the coating.

In the early years of film coating, the major process advantages resulted from the greater volatility of the organic solvents used. However, the use of such organic solvents has created many potential problems, including:

1. Flammability hazards.
2. Toxicity hazards.
3. Concerns over environmental pollution.
4. Cost (either relating to minimizing items 1–3, or to the cost of the solvents themselves).

However, since the initial introduction of film coating, significant advances have been made in process technology and equipment design. The emphasis has changed from needing highly volatile organic solvents (to achieve rapid drying), to attaining the same ultimate effect by designing equipment to have more efficient drying characteristics.

Thus, there has been a transition from conventional pans to side-vented pans and fluid-bed equipment, and consequently from the problematic organic solvent-based process to an aqueous one.

Film Coating Raw Materials—The major components in any film-coating formulation consist of a polymer, plasticizer, colorant and solvent (or vehicle).

Ideal properties for the polymer include solubility in a wide range of solvent systems to promote flexibility in formulation, an ability to produce coatings which have suitable mechanical properties and the appropriate solubility in gastrointestinal fluids such that drug bioavailability is not compromised.

Cellulose ethers are the preferred polymers in film coating, particularly hydroxypropyl methylcellulose. Suitable substitutes are hydroxypropyl cellulose, which may produce slightly tackier coatings, and methylcellulose, although this has been reported to retard drug dissolution.[10] Alternatives to the cellulose ethers are certain acrylics, such as methacrylate and methyl methacrylate copolymers.

Most polymers are employed as solutions in either aqueous or organic solvent-based systems. Alternative systems employ aqueous dispersions of water-insoluble polymers (eg ethylcellulose). Such systems usually are combined with aqueous solutions of water-soluble polymer in order to facilitate rapid drug release.

Many of the commonly used polymers are available in a range of molecular-weight grades, a factor which also must be considered in the selection process. Molecular weight may have an important influence on various properties of the coating system and its ultimate performance, such as solution viscosity and mechanical strength and flexibility of the resultant film.

The incorporation of a plasticizer into the formulation improves the flexibility of the coating, reduces the risk of the film cracking and possibly improves adhesion of the film to the substrate. To ensure that these benefits are achieved, the plasticizer must show a high degree of compatibility with the polymer, and be retained permanently in the film, if the properties of the coating are to remain consistent on storage. Examples of typical plasticizers include glycerin, propylene glycol, polyethylene glycols, triacetin, acetylated monoglyceride, citrate esters (eg, triethyl citrate) or phthalate esters (eg, diethyl phthalate).

Colorants usually are used to improve the appearance of the product as well as to facilitate product identification. Additionally, certain physical properties of the coating (eg its performance as a moisture barrier) may be improved. As in the case of sugar coating, colorants can be classified either as water-soluble dyes or insoluble pigments.

The use of water-soluble dyes is precluded with organic solvent-based film coating because of the lack of solubility in the solvent system. Thus, the use of pigments, particularly aluminum lakes, provides the most useful means of coloring film-coating systems. Although it may seem obvious to use water-soluble dyes in aqueous formulations, the use of pigments is preferred, since:

1. They are unlikely to interfere with bioavailability[11] as do some water-soluble dyes.
2. They help to reduce the permeability of the coating to moisture.[12]
3. They serve as bulking agents to increase the overall solids content in the coating dispersion.
4. They tend to be more light stable.

The major solvents used in film coating typically belong to one of these classes: alcohols, ketones, esters, chlorinated hydrocarbons and water. Solvents serve to perform an important function in the film-coating process, since they aid in the application of the coating to the surface of the substrate. Good interaction between solvent and polymer is necessary to ensure that optimal film properties are obtained when the coating dries. This initial interaction between solvent and polymer will yield maximum polymer-chain extension, producing films having the greatest cohesive strength and, thus, the best mechanical properties. An important function of the solvent systems also is to assure a controlled deposition of the polymer onto the surface of the substrate so that a coherent and adherent film coat is obtained.

Although it is very difficult to give typical examples of film-coating formulations, since these will depend on the properties of the materials used, such formulations usually are based on 5 to 15% (*w/w*) coating solids in the requisite vehicle (with the higher concentration range preferred for aqueous formulations), of which 60 to 70% is polymer, 6 to 7% is plasticizer and 20 to 30% is pigment.

Modified-Release Film Coatings

Film coatings can be applied to pharmaceutical products in order to modify drug release. The USP describes two types of modified-release dosage forms, namely those that are *delayed release* and those that are *extended release*. Delayed-release products often are designed to prevent drug release in the upper part of the gastrointestinal (GI) tract. Film coatings used to prepare this type of dosage form are commonly called *enteric coatings*. Extended-release products are designed to extend drug release over a period of time, a result which can be achieved by the application of a *sustained-* or *controlled-release* film coating.

Enteric Coatings—Enteric coatings are those which remain intact in the stomach, but will dissolve and release the contents of the dosage form once it reaches the small intestine. The purpose of an enteric coating is to delay the release of drugs which are inactivated by the stomach contents, (eg, pancreatin, erythromycin) or may cause nausea or bleeding by irritating the gastric mucosa (eg, aspirin, steroids). In addition, such coatings can be used to give a simple repeat-action effect where additional drug that has been applied over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract.

The action of enteric coatings results from a difference in composition of the respective gastric and intestinal environments in regard to pH and enzymatic properties. Although there have been repeated attempts to produce coatings which are subject to intestinal enzyme breakdown, this approach is not popular since enzymatic decomposition of the film is rather slow. Thus, most currently used enteric coatings are those which remain undissociated in the low pH environment of the stomach, but readily ionize when the pH rises to about 4 or 5. The most effective enteric polymers are polyacids having a pK_a of 3 to 5. Coatings subject to enzymatic breakdown are being considered now as protective coatings suitable for the colonic delivery of polypeptide drugs.

Historically, the earliest enteric coatings used formalin-treated gelatin, but this was unreliable since the polymerization of gelatin could not be controlled accurately, and often resulted in failure to release the drug, even in the lower intestinal tract. Another early candidate was shellac, but again the main disadvantage resulted from further polymerization that occurred on storage, often resulting in failure to release the active contents. Pharmaceutical formulators now prefer to use synthetic polymers to prepare more effective enteric coatings.

The most extensively used synthetic polymer is cellulose acetate phthalate (CAP) which is capable of functioning effectively as an enteric coating. However, a pH greater than 6 usually is required for solubility and thus a delay in drug release may ensue. It also is relatively permeable to moisture and gastric fluid compared to most enteric polymers. Thus it is susceptible to hydrolytic decomposition where phthalic and acetic acids are split off, resulting in a change in polymeric, and therefore enteric, properties.

Another useful polymer is polyvinyl acetate phthalate (PVAP) which is less permeable to moisture and gastric fluid, more stable to hydrolysis and able to ionize at a lower pH, resulting in earlier release of actives in the duodenum.

Other suitable enteric polymers include hydroxypropyl methylcellulose phthalate (which has properties similar to PVAP); methacrylic acid—methacrylic acid ester copolymers (some of which have a high dissociation constant[13]); cellulose acetate trimellitate (CAT, which has properties similar to CAP); carboxymethyl ethylcellulose (CMEC) and hydroxypropyl methylcellulose acetate succinate (HPMCAS).

Various systems recently have been introduced that allow many of these enteric polymers to be applied as aqueous dispersions, thus facilitating the use of aqueous film-coating technology for the enteric coating of pharmaceutical dosage forms.

Sustained-Release Coatings—The concept of sustained release formulations was developed in order to eliminate the need for multiple dosage regimens, particularly for those drugs requiring reasonably constant blood levels over a long period of time. In addition, it also has been adopted for those drugs which need to be administered in high doses, but where too rapid a release is likely to cause undesirable side effects (eg, the ulceration that occurs when potassium chloride is released rapidly in the gastrointestinal tract).

Formulation methods used to obtain the desired drug availability rate from sustained-action dosage forms include

1. Increasing the particle size of the drug.
2. Embedding the drug in a matrix.
3. Coating the drug or dosage form containing the drug.
4. Forming complexes of the drug with materials such as ion-exchange resins.

Only those methods which involve some form of coating fall within the scope of this chapter.

Materials which have been found suitable for producing sustained-release coatings include

1. Mixtures of waxes (beeswax, carnauba wax, etc) with glyceryl monostearate, stearic acid, palmitic acid, glyceryl monopalmitate and cetyl alcohol. These provide coatings which are dissolved slowly or broken down in the GI tract.
2. Shellac and zein—polymers which remain intact until the pH of gastrointestinal contents becomes less acidic.
3. Ethylcellulose, which provides a membrane around the dosage form and remains intact throughout the gastrointestinal tract. However, it does permit water to permeate the film, dissolve the drug and diffuse out again.
4. Acrylic resins, which behave similarly to ethylcellulose as a diffusion-controlled drug-release coating material.
5. Cellulose acetate (diacetate and triacetate).
6. Silicone elastomers.

As with an enteric coating, many of the synthetic polymers suitable for sustained-release film coating have been prepared as aqueous polymer dispersions (often called latexes or pseudolatexes) that are commercially available and facilitate the use of aqueous film-coating technology for the preparation of extended-release products.[14]

Various methods have been used to prepare sustained-release products using film-coating techniques. Examples include the application of suitable film coatings to

1. Dried granules (either irregular or spheronized).
2. Drug-loaded beads (or nonpareils).
3. Drug crystals.
4. Drug/ion-exchange-resin complexes.
5. Tablets.

In the first four examples, the final coated particles may either be filled into two-piece hard-gelatin capsules or compacted into tablets. Additionally, coated drug/ion-exchange resin complexes may be dispersed in viscous liquids to create liquid suspensions.

A rather unique application of the film-coated, sustained-release tablet is the elementary osmotic pump. In this device, a tablet core (formulated to contain osmotically active ingredients) is film coated with a semipermeable membrane which is subsequently "pierced" with a laser to create a delivery orifice. On the ingestion of such a device, the infusion of water generates an osmotic pressure within the coated tablet that "pumps" the drug in solution out through the orifice.

With sustained-release products, one must remain aware constantly of the fact that the final dosage forms typically contain drug loadings that are sufficiently high to cause problems if the entire dose is released quickly. This phenomenon, commonly called "dose-dumping," can be avoided only if:

1. The film coating is mechanically sound and will resist rupture on ingestion of the dosage form.
2. Sufficient coating is applied uniformly across the surface of the material that is to be coated.

Film-Coating Problems

As with sugar coating, difficulties may develop during, or subsequent to, the film-coating process. The tablets being coated may not be sufficiently robust, or may have a tendency to *laminate* while being coated. Since film coats are relatively thin, their ability to hide defects is significantly less than with sugar coating. Hence, tablets which have poor resistance to abrasion (ie, they exhibit high friability characteristics) can be problematic, since the imperfections readily may be apparent after coating. It is very important to identify tablets with suspect properties, whether mechanically or performance related (eg, poor dissolution), prior to a coating process, since subsequent recovery or reworking of tablets may be extremely difficult after a coating has been applied.

Various process-related problems can occur during the application of a film coating. One example is *picking*, which is a consequence of the fluid delivery rate exceeding the drying capacity of the process, causing tablets to stick together and subsequently become broken apart. Another example, *orange peel* or *roughness*, is usually the result of premature drying of atomized droplets of solution, or it may be a consequence of spraying too viscous a coating solution such that effective atomization is difficult.

Mottling, or lack of color uniformity, can result from uneven distribution of color in the coating, a problem often related to the use of soluble dyes in aqueous film coating when color migration can occur, either by evolution of residual solvent in the film, or by migration of plasticizer in which the colorant may be soluble. The use of pigments in the film-coating process minimizes the incidence of this latter objection considerably. However, uneven color also can result from poor pigment dispersion in the coating solution.

Finally, some major problems occur as the result of internal stress that develops within the film as it dries. One example is *cracking*, which occurs when this stress exceeds the tensile strength of the film. This problem may be compounded by postcompaction stress relaxation (a phenomenon that can occur with certain types of tablet formulations, such as those containing ibuprofen, after ejection from the die), which causes tablets to expand. Another example is *logo-bridging* (ie, bridging of a monogram present in the surface of the tablet core), which occurs when a component of the internal stress is able to overcome the adhesive bonds between the coating and the tablet surface, causing the film to pull away so that legibility of the monogram is lost. An understanding of the properties of the various ingredients used in the film-coating formulation, and how these ingredients interact with one another, can allow the formulator to avoid many of these internal-stress related problems.[15]

Coating Procedures and Equipment

Coating Pans—Sugar coating historically has involved the ladling of the various coating fluids onto a cascading bed of tablets in a conventional coating pan (Fig 1), fitted with a means of supplying drying air to the tablets and an exhaust to remove moisture and dust-laden air from the pan.

Typically, after the requisite volume of liquid has been applied, an appropriate amount of time is allowed for the tablets to mix and permit the liquid to be dispersed fully throughout the batch. To facilitate the uniform transfer of liquid, the tablets often are "stirred" by hand, or in larger pans, by means of a rake, to overcome mixing problems often associated with "dead spots," an inherent problem associated with the use of conventional pans. Finally, tablets are dried by directing an air supply onto the surface of the tablet bed. Thus, sugar coating is somewhat of a sequential process consisting of consecutive cycles of liquid application, mixing and drying.

During the early history of film coating, the equipment used was adapted essentially from that already employed for sugar coating. Although ladling of coating liquids during the film-coating process has been practiced, usually the liquid is applied using a spray technique. Spray equipment used are essentially of two types:

1. Airless (or hydraulic) spray, where the coating liquid is pumped under pressure to a spray nozzle with a small orifice, and atomization of the liquid occurs as it expands rapidly on emerging from the nozzle. This is analogous to the effect achieved when one places one's finger over the end of a garden hose.
2. Air spray, whereby liquid which is pumped under little or no pressure to the nozzle is atomized by means of a blast of compressed air that makes contact with the stream of liquid as it passes through the nozzle aperture.

Airless-spray techniques typically are used in large-scale film-coating operations for organic solvents, while air-spray techniques are more effective in either a small-scale laboratory set-up or in the currently popular aqueous film-coating operations.

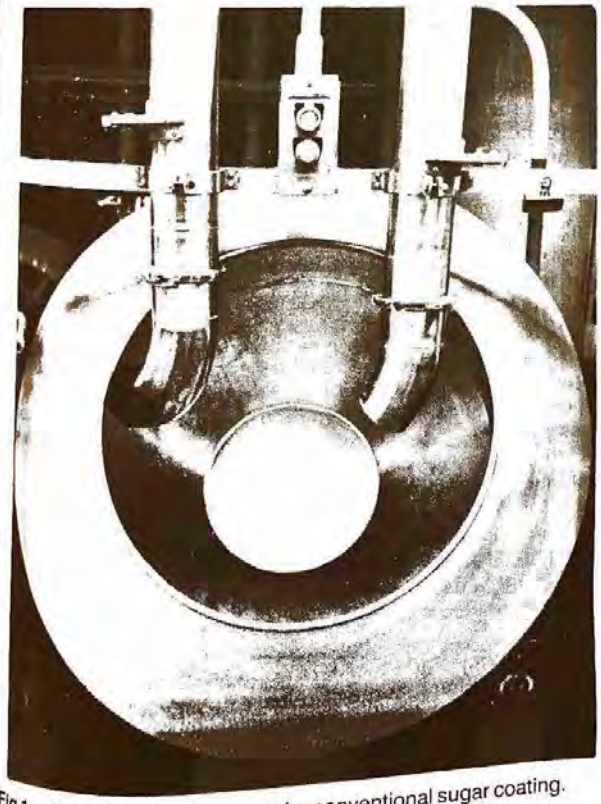


Fig 1. Typical equipment setup for conventional sugar coating.

The use of spray techniques permits the delivery of finely nebulized droplets of a coating solution to the moving tablet mass in such a manner as to ensure uniform coverage while preventing adjacent tablets from sticking together, as the coating solution rapidly dries. Although all the phases that occur during the spray process occur continuously and concurrently, the overall picture can be simplified and represented in the form of several sequential steps, as shown in Fig 2. The spray process can be operated either intermittently or continuously.

In the early years of film coating, the lack of adequate drying conditions inside the coating apparatus, together with the preference for using airless coating techniques (with their inherently higher delivery rates) with organic solvent-based formulations on a production scale, gave rise to the use of an intermittent spray procedure. This procedure allowed excess solvent to be removed during the nonspray part of the cycle, and thus reduced the risk of *picking* and the tendency for tablets to stick together. However, in later years, the improvement in drying capabilities has resulted in a continuous spray procedure being adopted, as this permits a more uniform coating to be developed and results in a shorter, simplified process.

As indicated previously, pan equipment initially was completely conventional in design and, with the exception of the addition of spray-application equipment, was similar to that used in sugar coating. Fortunately, film-coating formulations were based on relatively volatile organic solvents, which enabled acceptable processing times to be achieved in spite of the relative deficiencies of the air-handling systems. Since the equipment rarely represented a completely enclosed system, it did little to minimize the hazards of using organic solvents. Although conventional pans possessed acceptable properties with regard to mixing of the tablet mass in the sugar-coating process (particularly as this could be augmented by manual stirring of the tablets during processing), they were suited poorly to meet the more rigorous demands of the film-coating process, even when some simple form of baffle system was installed. In spite of these inadequacies, the use of conventional pans has persisted.

The introduction of aqueous film coating in recent years has presented the most serious challenge to conventional equipment. Limitations in both drying and mixing capabilities are likely to increase significantly the processing time and risk to product integrity when aqueous processes are used. Fortunately, these problems have been minimized as coating-pan design has evolved and improved.

Although considerable experimentation has taken place with the geometric design of conventional equipment, the most significant change came with the introduction of the Pellegrini coating pan (Fig 3), which is somewhat angular and rotates on a horizontal axis. The geometry of the pan, coupled with the fact that there is an integral baffle system, assures much more uniformity in mixing. Additionally, since the services are introduced through the rear opening, the front can either be left free for inspection purposes or simply closed off to yield

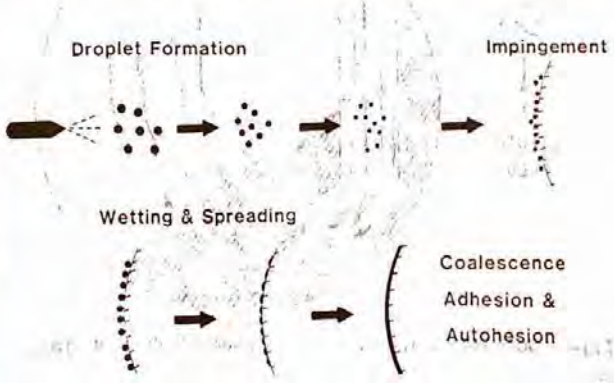


Fig 2. Schematic representation of the film-coating process.

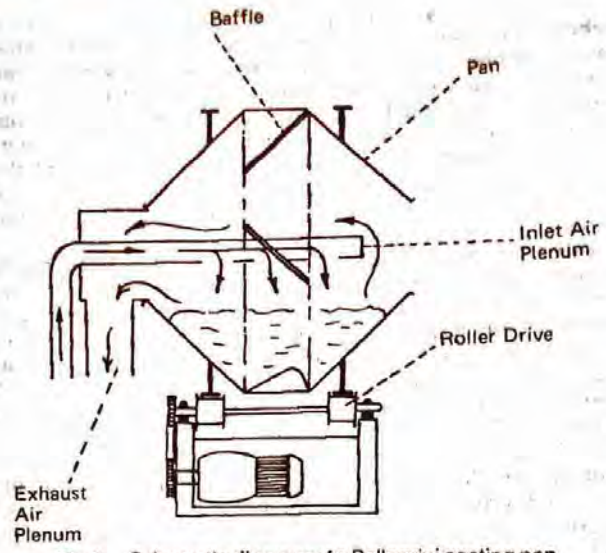


Fig 3. Schematic diagram of a Pellegrini coating pan.

an enclosed coating system. Although drying air is still applied only to the surfaces of the tablet bed, the other advantages derived from the basic overall design ensure that the Pellegrini pan is suitable more for film coating than the conventional equipment previously discussed. Currently, Pellegrini pans are available with capacities ranging from the 10-kg laboratory scale-up to 1000 kg for high-output production.

Considering the relative inefficiencies with equipment in which the majority of drying takes place on the surface of the tablet bed, several attempts have been made to improve air exchange, particularly within the tablet bed. The first to be available on a commercial scale was that developed by Strunck, which, by extending the drying air duct so that it is immersed in the tablet bed, creates a void within the tablet bed from a spraygun located in the opening of the supply air duct (Fig 4). Exhaust air is taken from the pan in a somewhat conventional manner.

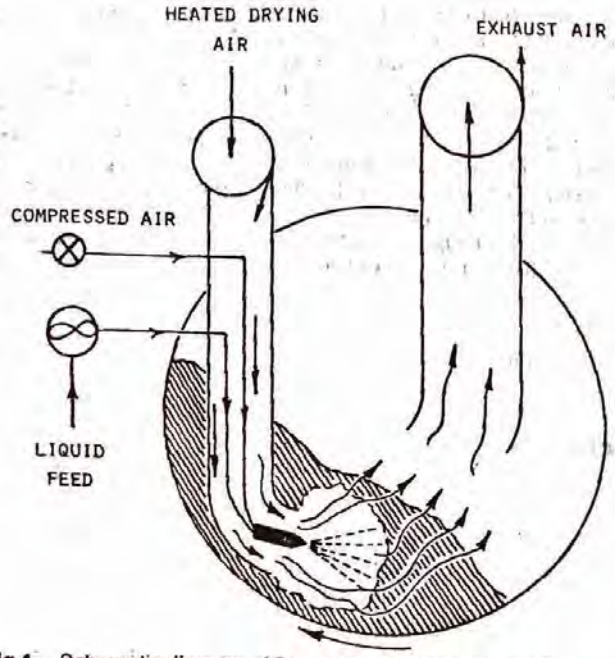


Fig 4. Schematic diagram of Strunck immersed-tube coating apparatus.

A second approach, called the Immersion Sword Process, uses a two-chamber system situated in the bed of tablets, enabling heated air to be introduced directly into the tablet bed through perforated air chambers. After interacting with the cascading bed of tablets, the air is drawn into a perforated exhaust air chamber for venting to the outside. This equipment currently is adaptable to both conventional and Pellegrini-type pans (see Fig 5). An alternative modification of the Pellegrini coating pan is provided by the GS coating system, which also allows drying to take place within the tablet bed. A similar approach is used with the Nicomac coating system.

A major advance in pan-coating technology occurred with the introduction of the side-vented pan concept, an innovation developed by Eli Lilly. Lilly's invention became the Accela-Cota, which is shown in Fig 6. The salient features of this design are

An angular pan (fitted with an integral baffle system) that rotates on a horizontal axis.

A coating system that is completely enclosed.

A perforated pan that allows drying air (that has been introduced into the pan) to be pulled through a cascading bed of tablets while the coating liquid is applied to the tablet surface using a spray-atomization technique.

This pan-coating design drastically improves the drying characteristics of the coating process, a feature which has been a major factor in the successful introduction of aqueous film-coating technology.

Since the introduction of the Accela-Cota, a variety of designs of side-vented coated pans have been introduced by major equipment vendors. A summary of many of these alternative designs is provided in Table 4.

Interesting features of side-vented coating pans in recent years include the fact that

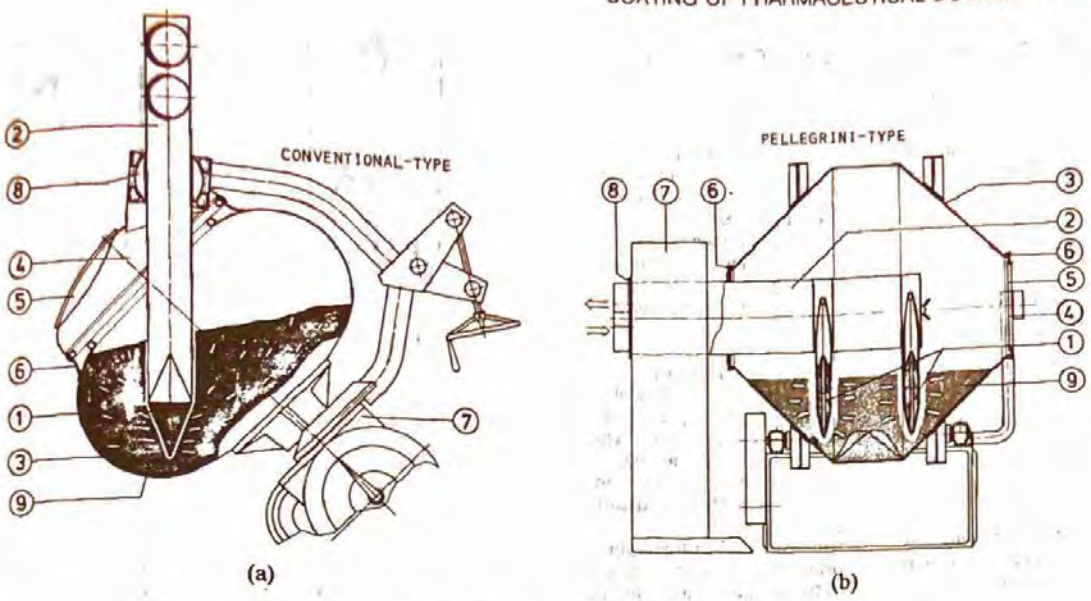
1. Designs have become more complex and now permit multidirectional air flow.
2. Fully-automated, computerized coating processes are becoming commonplace (especially for production-scale coating purposes).
3. Clean-in-place (CIP) systems also are becoming commonplace in order to facilitate compliance with GMPs.
4. Laboratory-scale coating equipment now is being provided with interchangeable coating pans representing batch-size capabilities in the range of 3 to 40 kg (depending on product density).

Although the evolution in coating-pan design has occurred predominately to facilitate use of the aqueous film-coating process, these advances in processing technology also have been of benefit to the sugar-coating process.

Fluidized-Bed Coating Equipment—Fluid-bed processing technology has been used in the pharmaceutical industry for a long time. While various attempts have been made to apply this technology to the film-coating process, a major development came with the introduction of the Wurster concept in the 1950s. A schematic of the Wurster process is shown in Fig 7.

When the use of organic-solvent-based coating formulations was in its heyday, the Wurster process was extremely popular for coating a variety of pharmaceutical dosage forms, especially tablets. Although fluid-bed processing inarguably possesses the greatest potential to achieve effective drying, the growing interest in the use of aqueous coating formulations has been accompanied surprisingly by a waning interest in using the Wurster process for coating tablets. A major factor in this trend undoubtedly is related to the greater potential (compared to when coating pans are used) for tablet breakage in the fluid-bed process. During the last 15 years, however, a resurgent interest in the Wurster process has occurred as a result of the growing demand for applying film coatings to pellets, granules and powders (so-called *multiparticulates*) in order to prepare modified-release dosage forms.

The suitability of the fluid-bed process for film coating multiparticulates also has generated interest in processes other than the Wurster for this application. In particular, a modi-



Key: 1. Immersion Sword
2. Coaxial conduit
3. Coating pan
4. Pan cover
5. Clear control cover
6. Silicone seal
7. Stand
8. Coaxial conduit adjustment
9. Coating bed

Fig 5. Schematic diagram of the immersed-sword apparatus for use in either (a) a conventional pan or (b) a Pellegrini pan.

cation of the spray granulation process (often termed the *top-spray coating process*) and a rotary process (often called the *tangential spray process*) have both been used for the film coating of multiparticulates. Schematics for all these processes also are shown in Fig 7.

The three major manufacturers of fluid-bed processing equipment (Glatt Air Techniques, Vector Corporation and Niro-Aeromatic) all have adopted the principle in which a basic processing unit has been designed to accept modular inserts for each of the three fluid-bed coating processes shown

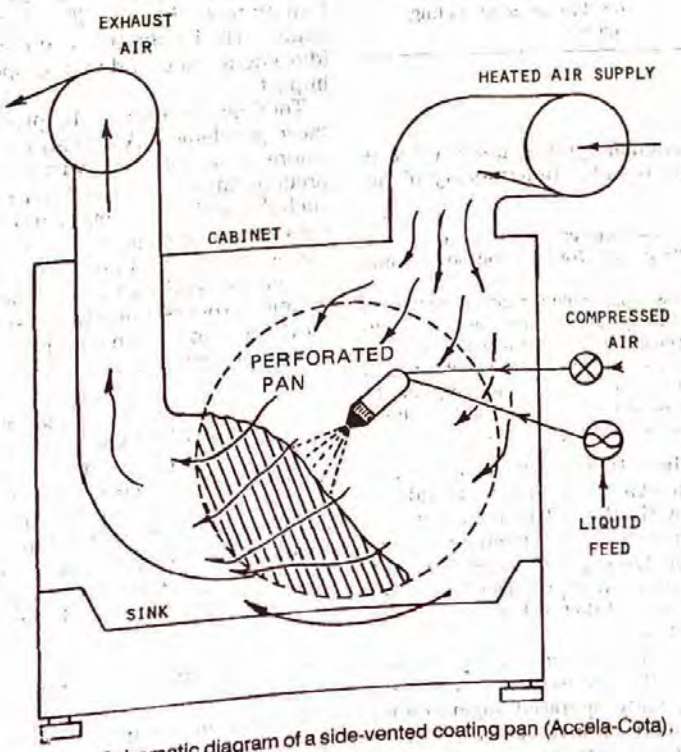


Fig 6. Schematic diagram of a side-vented coating pan (Accela-Cota).

Table 4—Examples of Side-Vented Coating Pans

Pan	Manufacturer	Comments
Accela-Cota	Thomas Engineering Hoffman Estates, IL	The first side-vented pan. Cylindrical portion of pan is fully perforated. Exhaust plenum is located below tablet bed; inlet air plenum is located diametrically opposite (See Fig 6).
Fast Coater	O'Hara Manufacturing Ltd, Toronto, Canada	Operating principle similar to Accela-Cota.
Hi-Coater	Vector Corp. Marion, IA	Drying air introduced via a plenum in front opening of pan. Cylindrical portion of pan is perforated in four segments (located 45° apart) which are linked via ducts on outside of pan to the exhaust plenum.
Driacoater	Driam Metallprodukt GmbH, Eriskirch, Germany	A nonagonal (rather than cylindrical) pan with each segment of the pan having a perforated section. One of the first pans to introduce the multidirectional air-flow concept.
IDA-X	Dumoulin, La Varenne, France	A fully-perforated pan (similar to Accela-Cota). Also uses the multidirectional air-flow concept.
Pro Coater	Glatt Air Techniques, Ramsey, NJ	A fully-perforated pan (similar to Accela-Cota). However, although exhaust plenum is located beneath the tablet bed (8-o'clock position), the inlet on plenum is located in the 4-o'clock position.
Butterfly	Hüttlin, Steinen, Germany	Not a perforated pan. Uses specially engineered slotted openings (at junction of pan-end wall and cylindrical portion of pan) to permit exhausting.
BSC	CMS Ames, IA	A fully perforated pan (similar to Accela-Cota) originally developed for the seed-coating industry.

in Fig 7. Selection of a particular type of insert often is determined by the nature and intended functionality of the coating applied; for example

1. Granulator Top-Spray Process—preferred when a taste-masking coating is being applied; additionally suitable for the application of hot-melt coatings.
2. Wurster, Bottom-Spray Process—preferred for the application of modified-release coatings to a wide variety of multiparticulates; also suitable for drug layering when the drug dose is in the low-to-medium range.
3. Rotor, Tangential-Spray Process—suitable for the application of modified-release film coatings to a wide range of multiparticulate products. Ideal for drug layering when the dose is medium-to-high. Also useful as a spheronizing process for producing spheres from powders.

While the general trend has been to use equipment employing this modular concept, an innovative approach to fluid-bed film coating was introduced by Hüttlin. This company created a design known as the Kugel coater,[16] a machine that has three basic configurations: the *Duo*, *Quattro* and *Turbojet*. The first two configurations are designed primarly for coating granules, pellets and small tablets, while the Turbojet is more suitable for coating regular tablets.

Potential for Totally Automated Coating Systems—During the last few decades, the industry has witnessed a general transition from manually operated sugar-coating procedures, requiring total operator involvement, to film-coating ones in which operator intervention is infrequent.

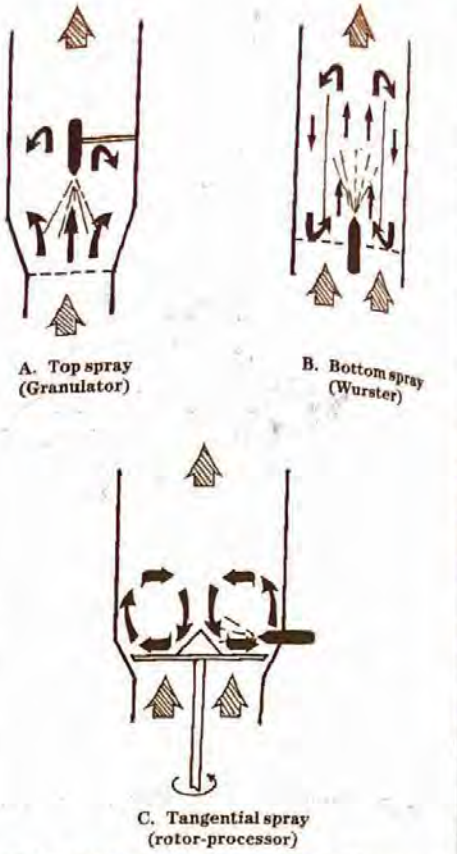


Fig 7. Schematic diagrams for three basic processes used in fluid-bed film coating.

Increasing familiarity with, and understanding of, tablet coating as a unit process, and a desire to ensure compliance with GMPs, ultimately have increased the desire for assuring conformity to design specifications for every batch of product made. Obviously, this is difficult for any process where the idiosyncracies of individual operators can have a significant impact.

Total automation of the process can provide a solution to these problems. Automation involves developing a process where all the important variables and requisite constraints are predetermined. These then can be translated into a form such that ultimate control and monitoring of the various process parameters can be maintained either by a microprocessor or central computer system. However, the system only will be as good as those peripheral devices used to detect various process conditions such as air flow, temperature, humidity, application volumes, delivery rates, etc.

Since a sugar-coating process always has been highly operator-dependent, removal of much of the operator intervention could be achieved by automation. Automation has, however, been complex because of the various sequences that occur and the variety of coating fluids used in a single sugar coating process. That it has been accomplished is evidenced by the number of commercially available systems which have been introduced.[17] The technology for automated control of both sugar- and film-coating processes has become very refined, and most major equipment suppliers are able to offer a coating process that is automated to various degrees (depending on end-user preferences).

Quality Control of Coated Tablets

The most important aspects of coated tablets which must be assessed from a quality-control standpoint are appearance characteristics and drug availability. From the appearance

standpoint, coated tablets must be shown to conform, where applicable, to some color standard, otherwise the dispenser and the consumer may assume that differences have occurred from previous lots, signifying a changed or substandard product. In addition, because of the physical abuse that tablets, both in their uncoated and coated forms, receive during the coating process, it is essential to check for defects such as chipped edges, picking, etc, and ensure they do not exceed predetermined limits.

Often, in order to identify the products, coated tablets may be imprinted (particularly with sugar-coated tablets) or bear a monogram (commonly seen with tablets that are film-coated). The clarity and quality of such identifying features must be assessed. The failure of a batch of coated tablets to comply with such preset standards may result in 100% inspection being required or the need for the batch to be reworked.

Batch-to-batch reproducibility for drug availability is of paramount importance, consequently each batch of product should be submitted to some meaningful test such as a dissolution test. Depending on the characteristics of the tablet core to be coated, tablet coatings can modify the drug-release profile, even when not intended (unlike the case of enteric- or controlled-release products). Since this behavior may vary with each batch coated (being dependent, for example, on differences in processing conditions or variability in raw materials used), it is essential that this parameter should be assessed, particularly in products that are typically borderline (refer to Chapter 92).

Stability Testing of Coated Products

The stability-testing program for coated products will vary depending on the dosage form and its composition. Many stability-testing programs are based on studies which have disclosed the conditions a product may encounter prior to end use. Such conditions usually are referred to as normal and include ranges in temperature, humidity, light and handling conditions.

Limits of acceptability are established for each product for qualities such as color, appearance, availability of drug for absorption and drug content. The time over which the product retains specified properties, when tested at normal conditions, may be defined as the *shelf-life*. The container for the product may be designed to improve the shelf-life. For example, if the color in the coating is light-sensitive, the product may be packaged in an amber bottle and/or protected from light by using a paper carton. When the coating is friable, resilient material such as cotton may be incorporated in both the top and bottom of the container, and if the product is affected adversely by moisture, a moisture-resistant closure may be used and/or a desiccant may be placed in the package. The shelf-life of the product is determined in the commercial package tested under normal conditions.

The stability of the product also may be tested under exaggerated conditions. This usually is done for the purpose of accelerating changes so that an extrapolation can be made early, concerning the shelf-life of the product. Although useful, highly exaggerated conditions of storage can supply misleading data for coated dosage forms. Any change in drug release from the dosage form is measured *in vitro*, but an *in vivo* measurement should be used to confirm that drug availability remains within specified limits over its stated shelf-life. This confirmation can be obtained by testing the product initially for *in vivo* availability and then repeating at intervals during storage at normal conditions for its estimated shelf-life (or longer).

Interpretation of stability data for coated, modified-release products should be undertaken with extreme care, since the diffusion characteristics of polymeric films can change significantly under exaggerated temperature conditions. This change may be confounding when trying to predict their diffusion characteristics under more moderate conditions and thus can prove misleading when predicting shelf life.

When elevated-temperature stability studies are conducted on products coated with aqueous polymeric dispersions (latexes or pseudolatexes), the data obtained might be more indicative of morphological changes that have occurred in the film. Such changes may result from partial destruction of the film when coated material adheres together in the container and subsequently is broken apart; additionally, these changes might result from further coalescence of the coating (which can occur when the coating is not coalesced completely during the coating process).

Stability tests usually are conducted on a product at the time of development, during the pilot phase and on representative lots of the commercial product. Stability testing must continue for the commercial product as long as it remains on the market because subtle changes in a manufacturing process and/or a raw material can have an impact on the shelf life of a product.

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CHAPTER 83

Preformulation

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The intelligent selection of new potential drug compounds from the discovery process, and their formulation into dosage forms with high and consistent bioavailability, is more important than ever in the pharmaceutical industry. Reasons for this importance include the time and expense required to discover and develop new drugs; the cost of drug substances; more drugs with solubility and bioavailability problems; the advent of highly potent biotechnology-derived proteins and peptides; lot-to-lot changes in the physical-chemical properties of drug substance and multisourcing of drug substance and drug product.

Statistics indicate that the odds of a new compound synthesized in the discovery process becoming a commercially viable drug product is less than 1 in 10,000. The reasons for these poor odds are many and include those of scientific and marketing origins. Included in the reasons is the selection of compounds for development that had unsuitable physical-chemical properties such as instability or insolubility that ultimately led to poor bioavailability or efficacy in human clinical studies. Solutions for these problems often are found in the preformulation process where the physical, chemical and mechanical properties of drug substances are determined.

The stage in the research and development process at which preformulation begins can greatly affect the odds of a new compound becoming a commercially viable drug product. In general, the sooner preformulation data is available, the earlier decisions can be made about the nature of the physical-chemical properties and how these might impact on the development potential of a new drug candidate. For example, when the preformulation scientist works closely with discovery scientists, preformulation data along with biological data can be used to select from a group of compounds, the best compound for future development. It is all too common that new compounds are chosen for development without adequate preformulation data. Hence, problems with stability, solubility and bioavailability occur in the dosage-form development process that could have been prevented or modified had preformulation data been part of the compound selection process.

The bioequivalency of multisource pharmaceutical products continues to receive great attention from practitioners and regulatory authorities alike. It is well documented that the bioavailability of certain drugs is very susceptible to the physical-chemical properties of the drug substance and the process and composition of the formulation. As a result, the efficacy of the formulations can vary dramatically. Even though this does not occur with all drugs, the manner in which the information has been reported by scientists often appears unclear to the practitioner. The information also has been interpreted differently depending on the motivation, viewpoint and attitude of the interpreter.

To optimize the performance of drug products, it is necessary to have a complete understanding of the physical-chemical and mechanical properties of drug substances prior to formulating them into drug products. The development of an optimum formulation is not an easy task, and many factors readily influence formulation properties. Drug substances rarely are administered as pure chemical entities, and are almost always given in a formulation containing excipients. The complexity of the formulation can vary from a simple aqueous solution to a complex controlled-release dosage form containing several polymeric materials. Sometimes the degree of complexity is determined by patent motivation, but more often it is determined by the properties that are expected from or built into the dosage form and by the resulting composition that is required to achieve these qualities.

The high degree of uniformity, physiological availability and therapeutic quality expected of modern medicinal products usually are the result of considerable effort and expertise on the part of the formulating pharmacist. These qualities are attained by careful selection and control of the quality of the various ingredients employed, appropriate manufacturing according to well-defined processes and, most importantly, adequate consideration of the many variables that may influence the composition, stability and utility of the product. In dealing with the formulation of new products it has become necessary to apply the best research methods and tools in order to develop, produce and control the potent, stable and effective dosage forms which make up our modern medical armamentarium.

The pharmaceutical formulator has a need for specialized areas of science in order to acquire and understand scientific information about the drug substance that is necessary to develop an optimum dosage form. The pharmaceutical industry no longer can rely only on past experience or empirical thinking to formulate dosage forms. Industry does not have the time or resources to operate by empirically putting dozens of formulations on a stability-testing schedule and waiting to see which were the most stable. Nor does it have the time or resources to test all these formulations for optimum bioavailability. In short, as much information must be acquired about the drug substance very early in its development. This requires an interdisciplinary approach during the preformulation exercise. Figure 1 shows how the development of a drug requires a multidisciplinary approach involving basic science during the preformulation phase followed by applied science during the development phase.

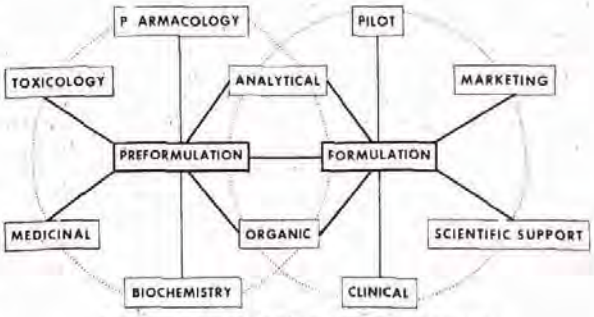

Fig 1. The wheels of product development.

This chapter will discuss the physical-chemical evaluation that takes place during the preformulation stage of development. In addition, consideration will be given to some specialized formulation ingredients that may require discretion in their selection.

Preformulation may be described as a phase of the research and development process where the preformulation scientist characterizes the physical, chemical and mechanical properties of a new drug substance, in order to develop stable, safe and effective dosage forms. Ideally, the preformulation phase begins early in the discovery process such that appropriate physical-chemical data is available to aid in the selection of new chemical entities that enter the development process. At this stage, experiments typically focus on salt selection and its effect on solubility and stability. In all likelihood, the lot sizes synthesized by the medicinal chemist at these early phases are on the order of 200 to 300 mg. Because the synthetic process is likely to change (especially the last step whereby the chemical is crystallized), properties such as crystal size and shape are not critical at this point. It also should be noted that solubility data, in particular, is useful to the pharmacologist and toxicologist in selecting solubilizing vehicles for efficacy and safety studies in animals. Many drug candidates are deemed unefficacious by pharmacology and/or safe by toxicology because of low solubility (and hence low bioavailability) in the dosing vehicles.

The bulk of preformulation work occurs after a new chemical entity and its appropriate salt form have been selected for testing in humans. The initial phase of this work focuses on the filing of an Investigational New Drug Application (INDA) and development of a dosage form for Phase 1 and early Phase 2 clinical studies. Since the odds are less than 1 in 10 that a drug entering Phase 1 clinical trials will proceed to the filing of a New Drug Application (NDA), the Phase 1 dosage form may not warrant the effort to give it the attributes of the market-image dosage form. In today's industrial environment it is imperative to move the drug into human clinical trials as soon as possible in order to determine if the candidate is a potential marketable drug. If the candidate is such a drug, a market-image dosage form can be developed after Phase 1 testing. For example, oral Phase 1 dosage forms are invariably powder-filled, hard-gelatin capsules because they can be easily blinded with respect to color, size and taste. Hence, preformulation studies at this phase of development should be designed to meet the needs of the initial INDA filing. Typical studies would include a pH-stability profile, a pH-solubility profile, studies for polymorphs, partitioning, dissolution behavior, crystal size and shape and compatibility with excipients to be used in the Phase 1 formulation. It should be noted that the lot size of drug substance is increasing at this stage of development, and the last step of the synthetic process may be defined. Therefore it is important to begin to gather historical data on lot-to-lot differences in physical properties, such as crystal habit or polymorphism.

A stability-indicating assay is very important. Typically high-performance liquid chromatography is the analytical method of choice, but development of the assay can take time and depends upon identification of the synthetic impurities and degradation products. In the meantime, thin-layer chromatography can be used to determine if a drug molecule is degrading. It is important for the preformulation scientist to work closely with the analytical chemists who support the synthetic chemists. Pooled effort can accelerate the analytical-methods development process by sharing information on synthetic impurities and degradation products. Accelerated conditions (heat, light, humidity) are used to promote degradation of the drug compound being evaluated. In order to identify and quantitate the mechanism of degradation, the degradation products must be identified and separable in the chromatographic procedure. This information is critical to the formulation scientist in order to stabilize the drug molecule in the dosage form.

During a preformulation study, it is necessary to maintain a high degree of flexibility. Problem areas must be identified early and focused upon. The preformulation scientist cannot afford to spend time generating data simply to check off activities on a check-list when the lack of other important data could significantly delay the development of a new drug. For example, selection of a suitable salt or polymorphic form is critical to the toxicology studies. If an unsuitable form is selected without careful preformulation testing, major portions of the toxicology program would have to be repeated. This could delay the overall development program by months or years, depending upon the phase of development in which the unsuitability is identified. Consequently, items such as salt form, hydrate form and polymorphic form are among the first items to be investigated.

When preformulation studies are initiated, the amount of drug substance usually is limited. The first supply of drug substance usually comes from the medicinal chemist where a typical lot size may be less than 1 g. For the remainder of preformulation studies, 25 to 150 g may be available from the chemical-development scientist. The medicinal chemist typically generates preliminary data such as melting point, spectral data and structure of the compound. The direction taken for preformulation is determined by the chemical structure of the new drug and the intended primary dosage forms to be developed. Many areas must be evaluated critically for each new drug substance, and it is essential that problem areas be identified early, otherwise delays could occur later in the development program. Some consequences of inadequate preformulation include possible use of unsatisfactory salt form, poor physical and chemical stability of the new drug substance, toxicological and clinical testing of compounds with marginal activity, increased development costs and increased development time. As preformulation studies progress, data is compiled, analyzed and transferred to scientists in discovery and development. In particular, the formulation scientist uses this information to develop dosage forms.

Physical Properties

Description

Since the pure drug entity is in short supply at the outset of most preliminary evaluations, it is extremely important to note the general appearance, color and odor of the compound. These characteristics provide a basis for comparison with future lots. During the preparation of scale-up lots the chemist usually refines or alters the original chemical synthetic route. This sometimes results in a change in some of the physical properties. When this takes place, comparisons can be made with earlier lots and decisions made regarding solvents for recrystallization.

Taste usually warrants some consideration, especially if the drug is intended for oral use in pediatric dosage forms. In such cases consideration should be given to the preparation of alternate salt forms or possible evaluation of excipients that mask the undesirable taste.

Microscopic Examination

Each lot of drug substance, regardless of size, is examined microscopically and a photomicrograph taken. The microscopic examination gives a gross indication of particle size and characteristic crystal properties. These photomicrographs are useful in determining the consistency of particle size and crystal habit from batch to batch, especially during the early periods of chemical synthesis; if a synthetic step is changed, they also give an indication of any effect the change may have on crystal habit. One must keep in mind that the photomicrograph only gives a qualitative indication of particle size distribution; it always is necessary to do a particle-size analysis for a more accurate picture of the distribution of particles in any particular batch of drug substance.

Particle Size

The uses of pharmaceutical products in a finely divided form are diverse. From knowledge of their particle size, such drugs as griseofulvin, nitrofurantoin, spironolactone, procaine penicillin and phenobarbital have been formulated so as to optimize activity. Other drugs, formulated in suspension or emulsion systems, in inhalation aerosols or in oral dosage forms, may contain finely divided material as an essential component. One of the basic physical properties common to all these finely divided substances is the particle-size distribution, ie, the frequency of occurrence of particles of every size. What is of practical interest usually is not the characteristics of single particles but rather the mean characteristics of a large number of particles. It must be emphasized, however, that knowledge of size characteristics is of no value unless adequate correlation has been established with functional properties of specific interest in the drug formulation. Many investigations demonstrating the significance of particle size are reported in the literature. It has been shown that dissolution rate, absorption rate, content uniformity, color, taste, texture and stability depend to varying degrees on particle size and distribution. In preformulation work it is important that the significance of particle size in relation to formulation be established early. Preliminary physical observations sometimes can detect subtle differences in color. If this can be attributed to differences in particle-size distribution, it is important to define this distribution and recommend that more attention be given to particle size in preparing future batches of drug substance. This effect also is evident when preparing suspensions of poorly soluble materials. One may observe batch-to-batch differences in the color of a suspension which can be related to differences in particle size. Sometimes, when small particles tend to agglomerate, a subtle change in color or texture may be evident.

Sedimentation and flocculation rates in suspensions are in part governed by particle size. In concentrated deflocculated suspensions the larger particles exhibit hindered settling and the smaller particles settle more rapidly. In flocculated suspensions the particles are linked together into flocs which settle according to the size of the floc and porosity of the aggregated mass. Flocculated suspensions are preferred since they have less tendency to cake and are more rapidly dispersible. Thus, it is apparent that the ultimate height, H_u, of sediment as a suspension settles depends on particle size. The ratio H_u/H_o, or the degree of suspendibility as affected by particle size, is valuable information for the formulator in order to prepare a satisfactory dosage form.

The rate of dissolution of small particles usually is faster than that of larger ones because rate of dissolution depends on the specific surface area in contact with the liquid medium. This usually is described by the modified Noyes-Whitney equation for dissolution rate dA/dt

$$\frac{dA}{dt} = KS(C_s - C) \qquad (1)$$

where A is the amount of drug in solution, K is the intrinsic dissolution rate constant, S is the surface area, C_s is the concentration of a saturated solution of the drug and C is the drug concentration at time t. The surface area of an object, regardless of shape, varies inversely with its diameter and confirms the above effect of particle size on dissolution rate. Solubility also has been observed to depend on particle size. Hussain demonstrated the power of a related equation, Fick's first law, for predicting the dissolution rates of slightly water-soluble powders.[1] Fick's first law can be written as

$$Q = (ASDt)/h$$

where Q = amount of drug (in grams) dissolved in time t, A = surface area occupied by total weight of the sample, S = solubility of the drug (g/mL) in dissolution media, D = diffusion coefficient of the drug (cm^2/sec) and h = thickness of the diffusional layer (cm).

By using experimentally determined values of 9×10^{-6} cm^2/sec and 50×10^{-4} cm for D and h, respectively, Hussain showed excellent correlation between dissolution rates calculated theoretically and those determined experimentally. Dittert, *et al*,[2] reported data for an experimental drug, 4-acetamidophenyl 2,2,2-trichloroethyl carbonate, which demonstrated that the dissolution rate and, in turn, bioavailability were affected by particle size. Although the ultimate amount of drug in solution may not be significant with respect to the dose administered, the formulator should be aware of this potential. With poorly soluble drugs it is extremely important to take these factors into account during the design of the dosage form. See also Chapter 34.

Flow properties of drugs can be influenced by particle size, and particle size reduction to extremely small sizes (less than 10 μm) may be inadvisable for some drug substances. Entrapped air adsorbed on the surface of the particles and/or surface electrical charges sometimes impart undesirable properties to the drug. For example, adsorbed air at the drug-particle surface may prevent wetting of the drug by surrounding fluid, and electrically induced agglomeration of fine particles may decrease exposure of the drug surface to surrounding dissolution medium. Such effects act as dissolution rate-limiting steps since they minimize maximum drug surface-liquid contact.

Crystal growth is also a function of particle size. Finer particles tend to dissolve and subsequently recrystallize and adhere to larger particles. This phenomenon is referred to as *Ostwald ripening*. Protective colloid systems can be used to suppress this nucleation. Preformulators can generate information concerning the effectiveness of different colloids that is extremely important to the formulator when he is given the task of preparing a suspension dosage form.

Particle-size reduction may be deleterious for some drug substances. Increasing surface area by milling or other methods may lead to rapid degradation of a compound. Drug substances also may undergo polymorphic transformation during the milling process. The preformulator must always be cognizant of these potential problems, and whenever the decision is made to reduce particle size, the conditions must be controlled and the stability profile evaluated. If a problem does arise, it is the responsibility of the preformulator to note it and attempt to resolve it prior to turning the drug substance over to the formulating pharmacist.

Gastrointestinal absorption of a poorly soluble drug may be affected by the particle-size distribution. If the dissolution rate of the drug is less than the diffusion rate to the site of absorption and the absorption rate itself, then the particle size of the drug is of great importance. Smaller particles should increase dissolution rate and, thus, bring about more rapid gastrointestinal absorption. One of the first observations of this phenomenon was made with sulfadiazine. Blood-level determinations showed that the drug in suspension containing particles 1 to 3 μm in size was absorbed more rapidly and more efficiently than from a suspension containing particles 7 times larger. Maximum blood levels were about 40% higher and occurred 2 hours earlier. Increased bioavailability with particle-size reduction also has been observed with griseofulvin. The extent of absorption of an oral dose increased 2.5 times when the surface area was increased approximately sixfold. Micronized griseofulvin permits a 50% decrease in dosage to obtain a satisfactory clinical response.

On the other hand, it was found that with nitrofurantoin there was an optimal average particle size that minimized side effects without affecting therapeutic response. In fact, a commercial product containing large particles is available. For chloramphenicol, particle size has virtually no effect on total absorption but it significantly affects the rate of appearance of peak blood levels of the drug. After administration of 50-μm particles, as well as 200-μm particles, peak levels occurred in 1 hour; with 400-μm particles peak levels occurred in 2 hours; with 800-μm particles peak levels occurred in 3 hours. All

four preparations had the same physiological availability, which implies that the absorption of chloramphenicol occurs uniformly over a major portion of the intestinal tract.

Reduction of particle size also may create adverse responses. For example, fine particles of the prodrug trichloroethyl carbonate were more toxic in mice than regular and coarse particles.[3] Increasing the surface area for water-soluble drugs, and possibly for weakly basic drugs, appears to be of little value. Absorption of weak bases usually is rate-limited by stomach emptying time rather than by dissolution. As previously mentioned, particle size is of importance only when the absorption process is rate-limited by the dissolution rate in gastrointestinal fluids.

The previous discussion considered the effect of particle size of the drug substance and its relationship to formulation. The particle size of the inert ingredients merits some attention. When one is concerned with particle size, all ingredients used in preparing the dosage form should be evaluated and some recommendation regarding their control should be made prior to full-scale development of a dosage form. It is recommended highly that particle size and its distribution be determined, optimized, monitored and controlled when applicable, particularly during early preformulation studies when the decision is made with regard to a suitable dosage form. The more common methods of determining particle size of powders used in the pharmaceutical industry include sieving, microscopy, sedimentation and stream scanning.

Sieving or Screening—Sieving or screening is probably one of the oldest methods of sizing particles and still is used commonly to determine the size distribution of powders in the size range of 325 mesh (44 μm) and greater. These data serve usually as a rough guideline in evaluating raw materials with regard to the need for milling. The basic disadvantages of screen analysis are the large sample size required and the tendency for blinding of the screens due to static charge or mechanical clogging. The advantages include simplicity, low cost and little skill requirement of the operator.

Microscopy—Microscopy is the most universally accepted and direct method of determining particle-size distribution of powders in the subsieve range, but this method is tedious and time-consuming. The preparation of the slide for counting particles is important because the sample must represent the particle-size distribution of the bulk sample. Extreme care must be taken in obtaining a truly representative sample from the bulk chemical. The cone and quartering technique usually gives a satisfactory sample. The sample should be properly suspended, dispersed and mixed thoroughly in a liquid which has a different refractive index from the particles being counted. A representative sample is mounted on a slide having a calibrated grid. For counting, random fields are selected on the slide and the particles are sized and counted. Between 500 and 1000 particles should be counted to make statistical treatment of the data meaningful.

The utility of microscopy has been enhanced greatly by the advent of computerized-image analysis systems. These systems give the operator the ability to observe the particles in the microscopic field, to consider particle-shape factors during measurement, to discriminate between drug and excipient particles and to remove operator bias during microscopic measurement. In addition, the computer provides sophisticated statistical analysis automatically, thereby eliminating manual tabulation and calculations. Computerized-image analysis systems can be validated fully and used on either pure drug substance or drug substance in the presence of excipients.[4]

Sedimentation—Sedimentation techniques utilize the dependence of velocity of fall of particles on their size. Application is made of the Stokes equation (see page 295) which describes a relationship between the rate at which a particle settles in a fluid medium to the size of that particle. Although the equation is based on spherical-shaped particles, it is used widely to determine the weight-size distribution of irregularly shaped particles. Data obtained by this procedure are usually reliable; however, the result may not agree with those obtained by other methods because of the limitations of the shape factor.

The *Andreasen Pipette Method* is used most commonly for sedimentation studies. Exact volumes are withdrawn at prescribed times and at a specified liquid depth. The liquid is evaporated and the residue of powder is weighed. The data are used in the Stokes equation and a weight-size distribution is calculated. Precautions must be observed with this method. Proper dispersion, consistent sampling, temperature control of the suspending medium and concentration should be achieved in order to obtain consistent results.

Stream Scanning—Stream scanning is a technique in which a fluid suspension passes through a sensing zone where the individual particles are electronically sized, counted and tabulated. The great advantage of this technique is that data can be generated in relatively short periods of time with reasonable accuracy. Literally thousands of particles can be counted in seconds and used in determining the size-distribution curve. The data are in a number of particles per class interval and can be expressed mathematically as the arithmetic mean diameter and graphed accordingly. Figure 2 illustrates a plot of typical data obtained for NBS Standard Reference Material No 1003.

The *Coulter Counter* and the *HIAC Counter* are used widely in the field of particle-size analysis in the pharmaceutical industry. They can be used to follow crystal growth in suspensions very effectively. Figure 3 shows the change in particle size with time for an aqueous suspension of Form I of an experimental drug. It appears that the growth of the particles decreases significantly after 6 hours. The photomicrograph shown in Fig 4 depicts the significant increase in particle size after 6 hours. Further treatment of the data as shown in Fig 5 enables one to establish rates of growth for suspended particles. Simply reading off the intercepts at the 1%, 2% or 3% oversize and plotting this increase in diameter with time enables one to calculate the rate of growth of particles in a suspension. This is shown in Fig 6.

Light Scattering—Light-scattering methods are generally fast, inexpensive and induce minimal artifacts. In general such methods operate by measuring light diffraction from suspended particles without forming an image of the particles onto a detector. A typical unit is the laser diffraction particle sizer (*Malvern*). In it, a liquid dispersion of particles flows through a beam of laser light. Light scattered by the particles and the unscattered remainder are incident onto a receiver lens that forms a diffraction pattern of the scattered

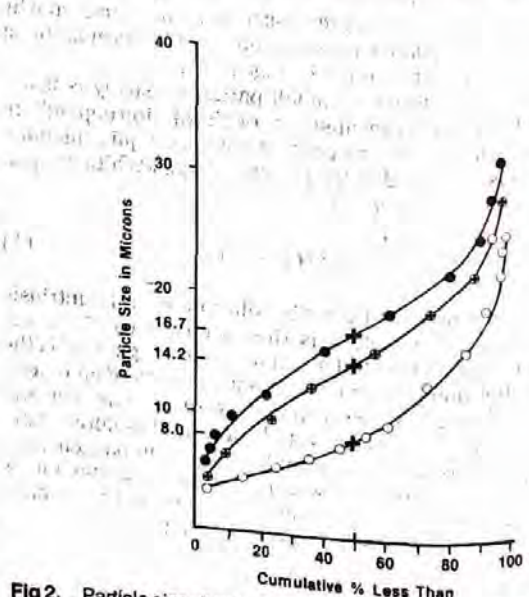

Fig 2. Particle size distribution of NBS glass beads (Standard Reference Material No 1003) expressed in terms of ○ = number of particles; ● = weight of particles; ⊗ = surface area of particles.

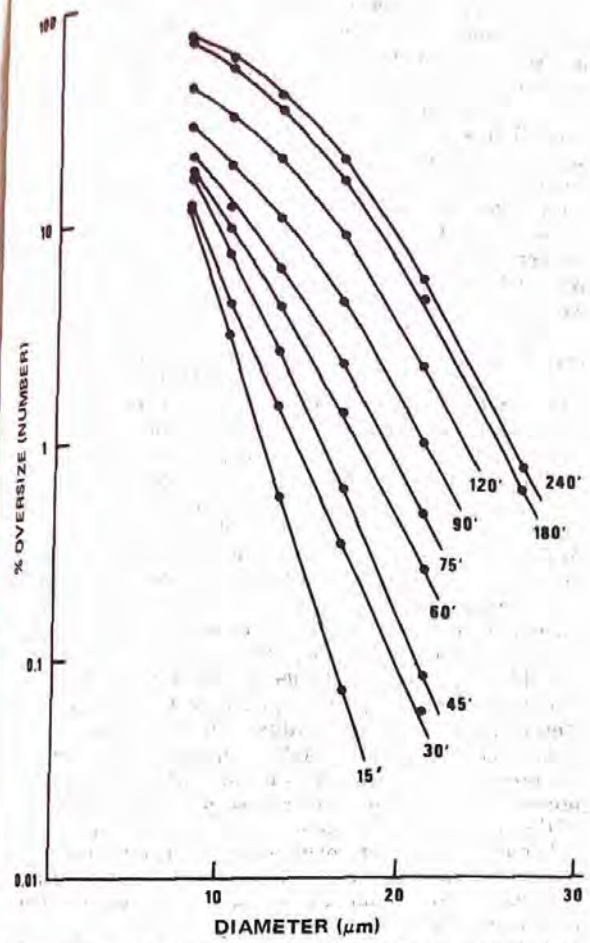

Fig 3. Change in particle size with time for an aqueous suspension of Form I of an experimental drug.

light. The scattered light and unscattered light then are gathered on detectors so the total light power is monitored as it allows the sample volume concentration to be determined. Each particle scatters light at a favored scattering angle that is related to its diameter. The detector provides an electronic output that makes it possible for a computer to deduce the volume-size distribution that gives rise to the observed scattering characteristics. Results may also be transformed to the equivalent surface or number distribution. Refer to Chapters 21 and 33.

Partitioning Effect

If an excess of liquid or solid is added to a mixture of two immiscible liquids, it will distribute itself between the two phases so that each becomes saturated. If the substance is added to the immiscible solvents in an amount insufficient to saturate the solutions, it still will distribute between the two layers in a definite concentration ratio. If C_1 and C_2 are the equilibrium concentrations of the substance in Solvent 1 and Solvent 2, the equilibrium expression becomes

$$\frac{C_1}{C_2} = k \qquad (2)$$

The equilibrium constant k is known as the distribution ratio or partition coefficient. Biologically, in order for a pharmacological response to occur, it is necessary that the drug molecule cross a biological membrane. The membrane, consisting of protein and lipid material, acts as a lipophilic barrier to most drugs. The resistance of this barrier to drug transfer is

FORM I

INITIAL SUSPENSION

FORM I

SUSPENSION AFTER 6 HOURS.

Fig 4. Photomicrographs showing change in crystal size for a suspension of Form I of an experimental drug.

related to the lipophilic nature of the molecule involved. See Chapter 41.

Understanding the partitioning effect and the dissociation constant enables one to estimate the site of absorption of a new chemical entity. If one assumes the stomach to have a pH range of 1.0 to 3.0 and the small intestines to have a pH range from 5 to 8, in most cases acidic drugs (pK_a 3) will be absorbed more rapidly in the stomach while more basic drugs (pK_a 8) will be absorbed more rapidly in the intestinal tract. There are exceptions, however. Some compounds have low

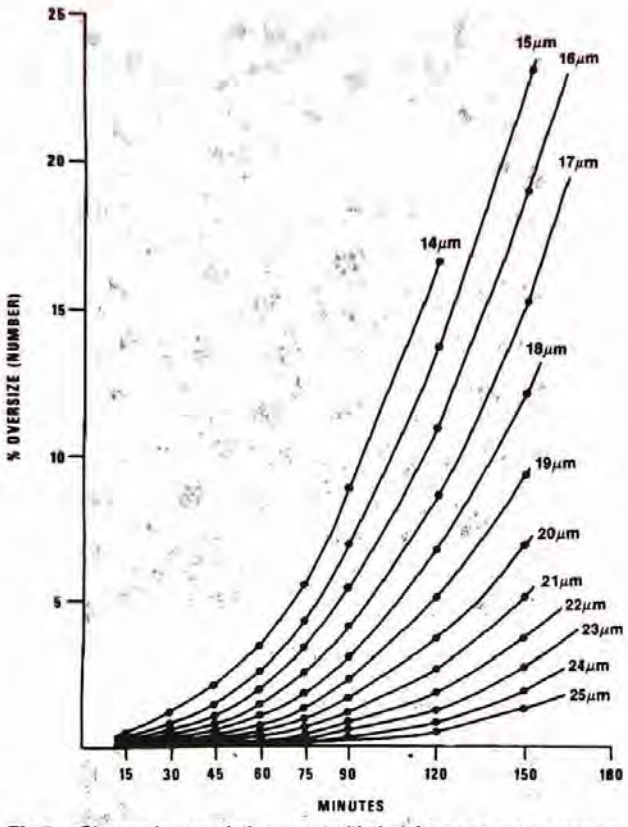

Fig 5. Change in cumulative count with time for an aqueous suspension of Form I of an experimental drug.

partition coefficients and/or are ionized highly over the entire physiological pH range, but still show good bioavailability.

Polymorphism

A polymorph is a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of the compound in the solid state. The molecule itself may be of different shape in the two polymorphs, but that is not necessary and, indeed, certain changes in shape involve formation of different molecules

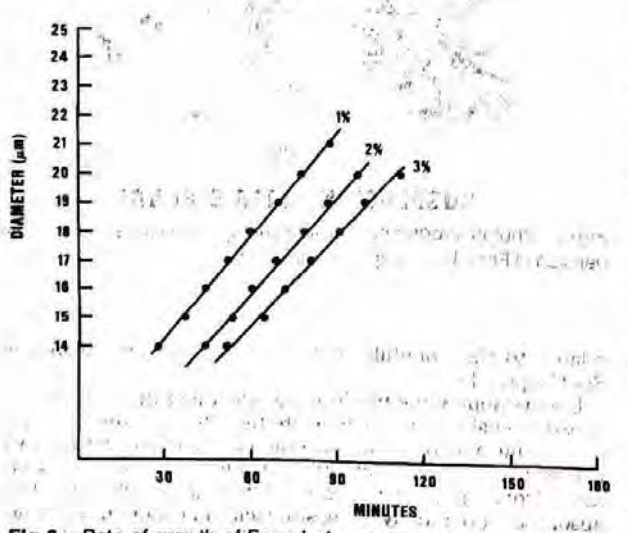

Fig 6. Rate of growth of Form I of experimental drug in aqueous suspension.

and, hence, do not constitute polymorphism. Geometric isomers or tautomers, even though interconvertible and reversibly so, cannot be called polymorphs although they may have in a confusingly similar manner.

A safe criterion for classification of a system as polymorphic is the following: two polymorphs will be different in crystal structure but identical in the liquid or vapor states. Dynamic isomers will melt at different temperatures, as do polymorphs, but will give melts of different composition. In time, each of these melts changes to an equilibrium mixture of the two isomers with temperature-dependent compositions. Some reported cases of polymorphism are undoubtedly dynamic isomerism, since the two behave quite similarly.

Polymorphism is the ability of any element or compound to crystallize as more than one distinct crystalline species, e.g. carbon as a cubic diamond or hexagonal graphite. Different polymorphs of a given compound are, in general, as different in structure and properties as the crystals of two different compounds. Solubility, melting point, density, hardness, crystal shape, optical and electrical properties, vapor pressure, stability, etc all vary with the polymorphic form. In general, it should be possible to obtain different crystalline forms of a drug substance exhibiting polymorphism and, thus, modify the performance properties for that compound. To do so requires a knowledge of the behavior of polymorphs. There are numerous reviews on the subject of polymorphism. In addition, numerous indications of the importance of polymorphism in pharmaceuticals are reported in the literature. Extensive studies of polymorphism have been conducted on steroids, barbiturates, antihistamines and sulfonamides. Preformulation usually includes rigorous studies to determine the presence of polymorphs in new drug substances being prepared for preliminary investigation in test animals. Some of the parameters routinely investigated are the number of polymorphs that exist, relative degree of stability of the various polymorphs, presence of a glassy state, stabilization of metastable forms, temperature stability ranges for each polymorph, solubilities, method of preparation of each form, effect of micronization or tableting and interaction with formulation ingredients.

The initial task of the preformulator is to determine whether or not the drug substance being evaluated exists in more than one crystalline form. The following procedures are usually followed to cause crystallization of a metastable form:[5]

1. Melt completely a small amount of the compound on a slide and observe the solidification between crossed polars. If, after spontaneous freezing, a transformation occurs spontaneously or can be induced by seeding or scratching, the compound probably exists in at least two polymorphic forms. It is essential to prevent nucleation of the stable form by inducing supercooling. Supercooling can be induced by using a small sample size, holding the melt for approximately 30 seconds about 10° above the melting point; carefully setting aside the compound without physical shock before observing it and rapid cooling of the compound.
2. Heat a sample of the compound on a hot stage and observe whether a solid-solid transformation occurs during heating.
3. Sublime a small amount of the compound and attempt to induce a transformation between the sublimate and the original sample by mixing the two in a drop of saturated solution of one of them. If the two are polymorphs, the more stable one will be more insoluble and will grow at the expense of the more soluble metastable form. This process will continue until the metastable form is transformed completely to the stable form. If the samples are not polymorphs, one may dissolve but the other will not grow. If the two are identical forms, nothing will occur.
4. Maintain an excess of the compound in a small amount of solvent held near the melting point of the compound. Isolate the suspended solid. Care should be taken to maintain the temperature during this step. Test the isolated material with an original sample using the procedure outlined in 3, above.
5. Recrystallize the compound from solution by shock-cooling, and observe a portion of the precipitated material suspended in a drop of the mother liquor. The drop then may be seeded with the original compound to check for solution-phase transformation. If the precipitate is a different polymorph, a solution-phase transformation should take place.

Once it has been established that polymorphism occurs, there are procedures which enable the preformulator to pre-

pare the various forms in larger quantities for further evaluation and suitability for incorporation into dosage forms.

Once a compound has been shown to exist in more than one crystalline form, a number of techniques are available to identify the different polymorphic phases present. Each of these techniques could be successful in identifying the phase, but a combination of methods provides a means for isolation and identification of each crystalline modification. In order to confirm the presence of more than one crystalline form of a compound, it is advisable to identify the modifications present by more than one method. Using only one method for confirming the presence of polymorphs sometimes may be misleading.

Microscopy—Optical crystallography is used in the identification of polymorphs. Crystals exist in isotropic and anisotropic forms. When isotropic crystals are examined, the velocity of light is the same in all directions, while anisotropic crystals have two or three different light velocities or refractive indices. This method requires the services of a trained crystallographer. Video recording systems have made it possible to record the events visualized during the heating and cooling stages, thereby providing a permanent record that can be re-examined.

Hot-Stage Methods—The polarizing microscope, fitted with a hot or cold stage, is very useful for investigating polymorphs. An experienced microscopist can tell quickly whether polymorphs exist: the degree of stability of the metastable forms; transition temperatures and melting points; rates of transition under various thermal and physical conditions and whether to pursue polymorphism as a route to an improved dosage form.

X-Ray Powder Diffraction—Crystalline materials in powder form give characteristic X-ray diffraction patterns made up of peaks in certain positions and varying intensities. Each powder pattern of the crystal lattice is characteristic for a given polymorph. This method has the advantage over other identification techniques in that the sample is examined as presented. Some care should be exercised in reducing and maintaining particle-size control. A very small sample size is needed and the method is nondestructive. This method has been used by several investigators in identifying polymorphs in pharmaceuticals.

Infrared Spectroscopy—This procedure is useful in identification of polymorphs. Solid samples must be used since polymorphs of a compound have identical spectra in solution. The technique can be used for both qualitative and quantitative identification.

Thermal Methods—Differential scanning calorimetry and differential thermal analysis have been used extensively to identify polymorphs. In both methods, the heat loss or gain resulting from physical or chemical transitions occurring in a sample is recorded as a function of temperature as the substance is heated at a uniform rate. Enthalpic changes, both endothermic and exothermic, are caused by phase transitions. For example, fusion, sublimation, solid-solid transition and water loss generally produce endothermic effects while crystallization produces exothermic effects. Thermal analysis enables one to calculate the thermodynamic parameters for the systems being evaluated. Heats of fusion can be obtained and the rate of conversion of polymorphs determined.

Dilatometry—Dilatometry measures the change in volume caused by thermal or chemical effects. Ravin and Higuchi[6] used dilatometry to follow the melting behavior of theobroma oil by measuring the specific volume of both rapidly and slowly cooled theobroma oil as a function of increasing temperature. The presence of the metastable form was shown by a contraction in the temperature range of 20 to 24°. This is illustrated in Fig 7. Dilatometry is extremely accurate; however, it is very tedious and time-consuming. It is not used widely.

Proton magnetic resonance, nuclear magnetic resonance and electron microscopy sometimes are used to study polymorphism.

Polymorphs can be classified into one of two types: (1) *enantiotropic*—one polymorphic form can be changed reversibly into another one by varying the temperature or pressure, eg, sulfur and (2) *monotropic*—one polymorphic form is unstable at all temperatures and pressures, eg, glyceryl stearates. At a specified temperature and pressure, only one polymorphic form will be thermodynamically stable. However, other metastable forms may exist under the same conditions. These metastable forms will convert to the stable lattice structures with time. The first indication of the significance of a polymorphic transformation in a pharmaceutical system was noted with novobiocin. The amorphous form of novobiocin was found to be well-absorbed; however, when formulated into a suspension, a reversion of the metastable form to the more stable crystalline form occurred resulting in poor absorption.

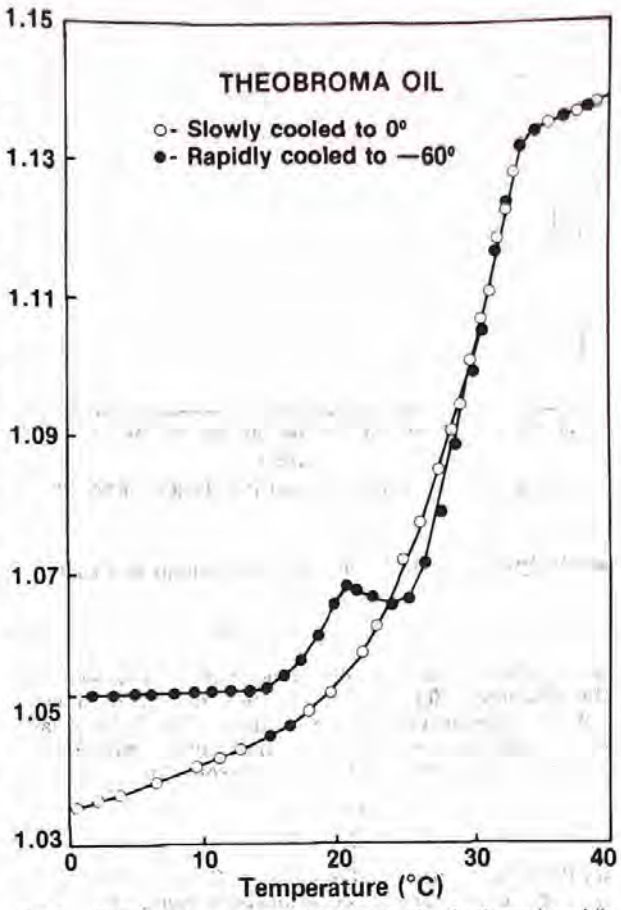

Fig 7. Dilatometric curves: theobroma oil, slowly and rapidly cooled.

After it has been determined that a drug substance does exist in more than one crystalline form, the conditions under which each can be produced should be established. In this manner, proper crystallizing conditions can be maintained from batch to batch to ensure a uniform and acceptable raw material. Recrystallization solvent, rate of crystallization and other factors may cause one crystal form to dominate. During the preliminary investigation to establish these conditions, it is necessary to monitor the forms prepared. For example, during the preliminary work with an indole derivative, differential scanning calorimetry, X-ray analysis and infrared analysis were used to establish that polymorphs were present and that they could be prepared satisfactorily. Figures 8, 9 and 10 show the respective data for this conclusion. When polymorphs are shown to be present, experiments should be designed to determine whether or not the properties differ sufficiently to alter their pharmaceutic or biologic behavior.

Dissolution tests can be used initially to show differences in apparent equilibrium solubilities provided a discriminating solvent system is used. Figure 11 illustrates dissolution data for two polymorphs of an indole derivative which had similar dissolution in the medium used; however, when a more discriminating dissolution medium was used, it was possible to show differences in their dissolution characteristics. This is illustrated in Fig 12. From the data presented for the indole derivative, it was concluded that there would be no appreciable difference in the availability of the two forms if they were to be administered orally in a solid dosage form. Subsequent testing in animals confirmed this. The Nernst equation relates the rate of concentration increase to the

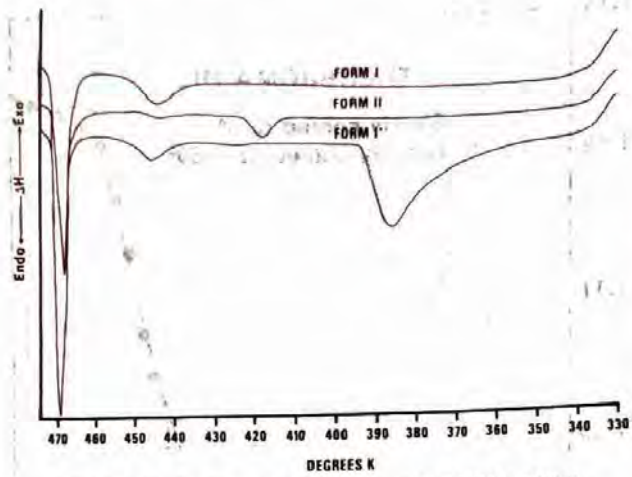

Fig 8. Thermograms for Forms I, I* and II of SK&F 30097.

solubility of a dissolving solid and is commonly written as

$$\frac{dc}{dt} = \frac{AD}{Vh}(C_s - C_t) \tag{3}$$

where A is the area of the dissolving interface of the solid, D is the diffusion coefficient of the solute in the solvent, V is the volume of the solvent, h is the thickness of the diffusion layer and C_s and C_t are concentration of the solute at saturation and at time t, respectively. The equation reduces to

$$\frac{dc}{dt} = \frac{AD}{Vh}C_s \tag{4}$$

for the experimental conditions where $C_s > C_t$. Since D is a property of the solute molecule and the solvent, it is independent of the solid-state form. The experimental conditions can be selected such that A, V and h can be maintained constant in measuring the dissolution rates of different polymorphic forms. The dissolution rate then is directly proportional to C_s, the saturation solubility, and the differences in the solubilities, can be related to their free energies.

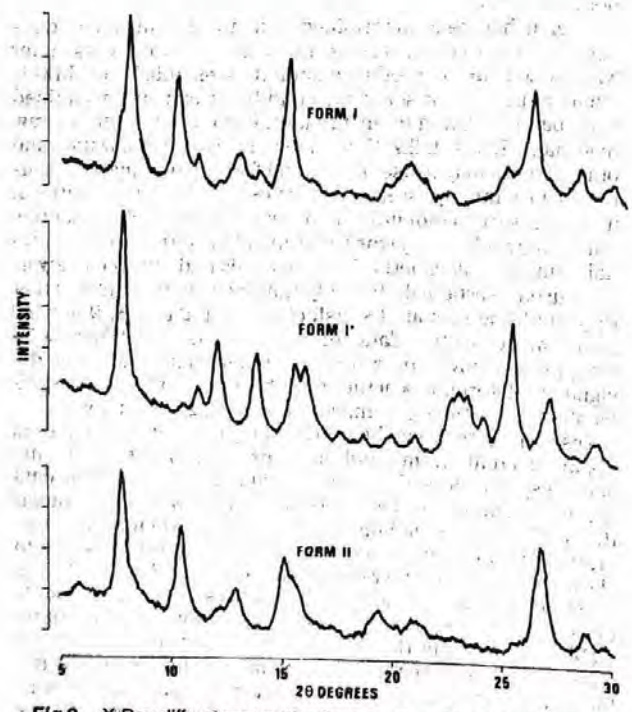

Fig 9. X-Ray diffractograms for Forms I, I* and II of SK&F 30097.

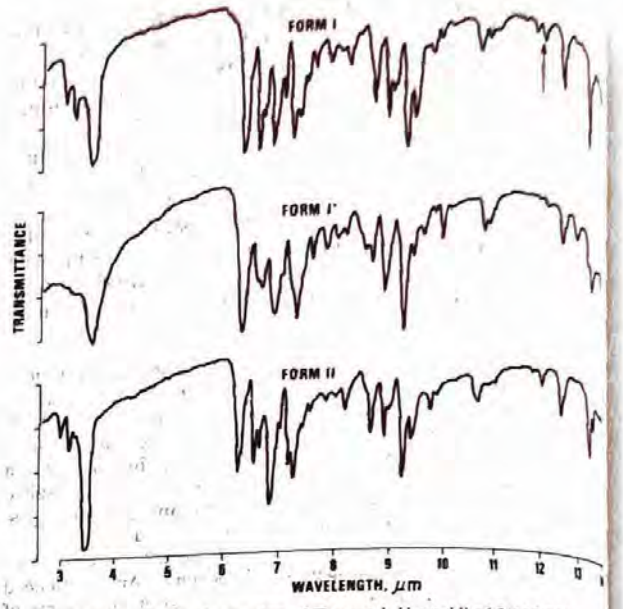

Fig 10. Infrared spectra of Forms I, I* and II of SK&F 30097.

The solubility and dissolution behavior of several polymorphs of chloramphenicol palmitate have been determined. Figures 13 and 14 illustrate the data obtained at several temperatures. It is apparent from the dissolution behavior that the maximum values obtained were good approximations of the solubility of the various forms. Therefore, obtaining data at several temperatures would enable one to calculate the thermodynamic quantities involved in the transition from the metastable to the stable form. A plot of the solubility data as a function of temperature in a typical van't Hoff fashion is

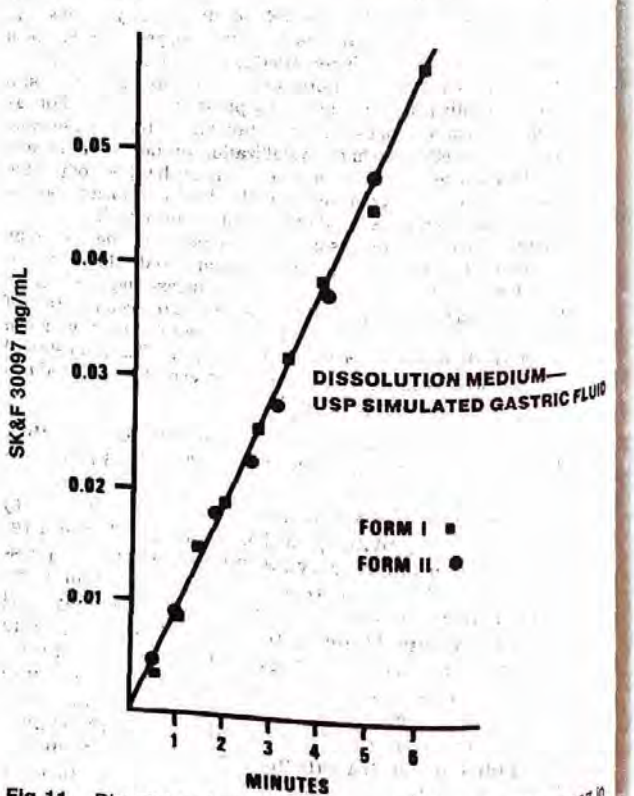

Fig 11. Dissolution behavior of Forms I and II of SK&F 30097 in artificial gastric fluid.

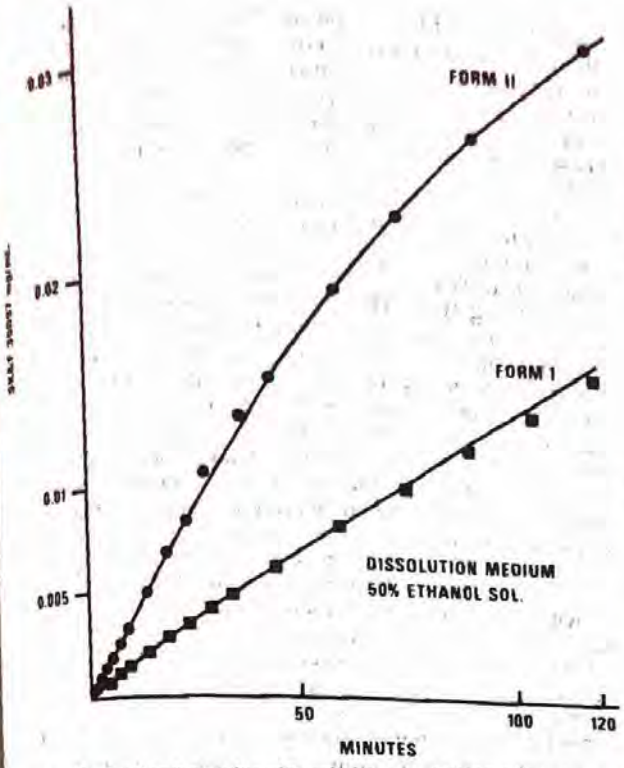

Fig 12. Dissolution behavior of Forms I and II of SK&F 30097 in 50% ethanol solution.

shown in Fig 15. The straight-line relationship enables one to calculate the heats of solution for the various forms and also, by extrapolation, to approximate the transition temperatures for the various forms. These values are shown in Table 1.[7]

At constant temperature and pressure, the free-energy differences between the polymorphs can be calculated by

$$\Delta G_t = RT \ln \frac{C_s \text{ Polymorph A}}{C_s \text{ Polymorph B}} \qquad (5)$$

This equation relates the solubility, C_s, of the polymorphic forms at a particular temperature, T, to the free energy differences, ΔG_t. Table 1 also contains the free-energy differences calculated for the polymorphs. The enthalpy changes also can be determined for the various transitions by subtracting the heat of solution derived for the stable form from that of the metastable form. Also, at any particular temperature, T, the entropy for the transition of polymorphs can be evaluated by the following relationship

$$\Delta S_t = \frac{\Delta H_{B \to A} - \Delta G_t}{T} \qquad (6)$$

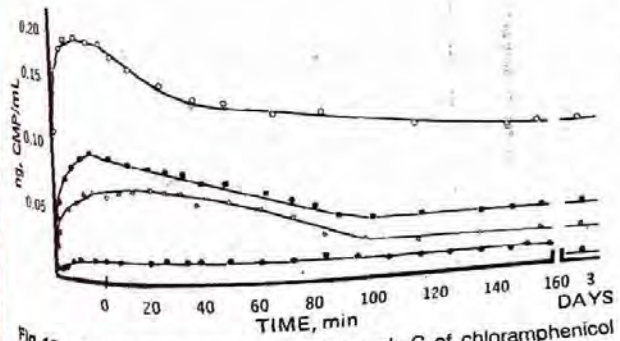

Fig 13. Dissolution curves for Polymorph C of chloramphenicol palmitate in 35% *t*-butyl alcohol and water at 30, 20, 15 and 6°. Key: 30°, ○—○; 20°, ■—■; 15°, △—△; 6°, ●—●.

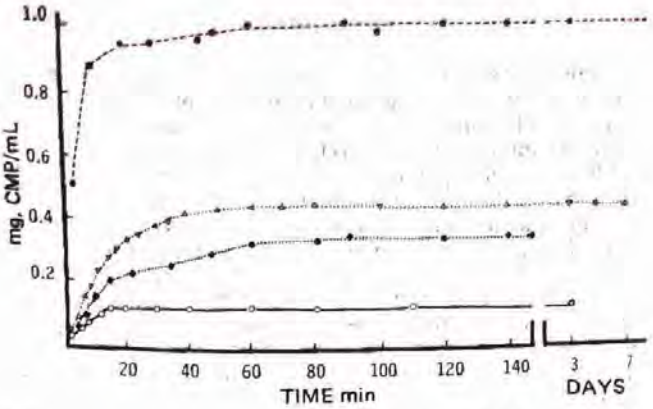

Fig 14. Dissolution curves for Polymorphs A and B of chloramphenicol palmitate in 35% *t*-butyl alcohol and water at 30 and 38°. Key: Polymorph A, 30°, ○—○; Polymorph B, 30°, △—△; Polymorph A, 38°, ◆- - -◆; Polymorph B, 38° ●—●.

The values computed for the transitions also are included in Table 1. At the transition temperature, ΔG_t is equal to zero and the entropy can be calculated, neglecting the free-energy term in Eq 6.

The thermodynamic relationships discussed are based on the assumption that Henry's law is obeyed. Knowledge of these thermodynamic relationships enables the preformulator to select more rationally the more energetic polymorphic form of the drug being investigated for further pharmacological studies and also to have a preliminary assessment of its probable stability.

When a preformulation group inadequately investigates polymorphic drug forms, problems may develop during the development stage. Crystal growth in suspensions resulting in poor uniformity, poor appearance, poor bioavailability, transformation occurring during milling or granulation resulting in changes in the physical and biological characteristics, inadequate pharmacological response and poor chemical stability are typical problems that may become evident.

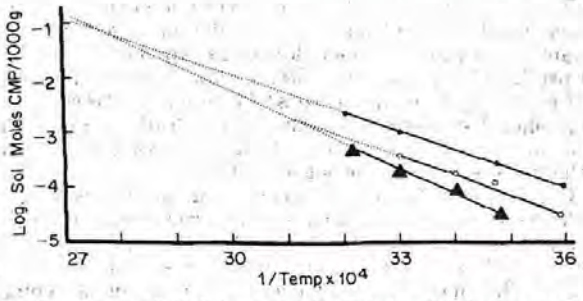

Fig 15. The van't Hoff type plot for Polymorphs A, B, and C of chloramphenicol palmitate. Key: Polymorphs A ▲; B ●—●; and C ○—○.

Table 1—Thermodynamic Values Calculated for Polymorphs *A*, *B* and *C* of Chloramphenicol Palmitate[7]

Polymorph	Transition temp. (°C) to form *A*	Heat of solution, kcal/mole	ΔG_t, cal/mole[a]	ΔS_{303} esu	ΔS_{trans} esu[a]
A	—	21.8	—	—	—
B	88	15.4	−774	−18	−17
C	50	17.2	−465	−13	−14

[a] Calculated for the conversion to Polymorph *A*.

Solubility

In dealing with new drug substances, it is extremely important to know something about their solubility characteristics, especially in aqueous systems since they must possess some limited aqueous solubility to elicit a therapeutic response. In addition, solubility information is critical to developing a discriminating dissolution test method. When a drug substance has an aqueous solubility less than 1 mg/mL in the physiological pH range (1 to 7), a potential bioavailability problem may exist and preformulation studies should be initiated to alleviate the problem. Equilibrium solubility of the drug substance should be determined in a solvent or solvent system which does not have any toxic effects on the test animal. This is done by placing an excess of drug in a vial with the solvent. The vial is agitated at constant temperature and the amount of drug determined periodically by analysis of the supernatant fluid. Equilibrium is not achieved until at least two successive samples have the same result. Experience with solubility determinations would indicate that equilibrium is usually attained by agitating overnight (approximately 24 hours). Solubility determinations can be conducted at several temperatures since the resultant drug products ultimately will be subjected to a wide variation in temperature.

If the solubility of the drug substance is less than the required concentration necessary for the recommended dose, steps must be taken to improve its solubility. The approach taken usually will depend on the chemical nature of the drug substance and the type of drug product desired. If the drug substance is acidic or basic, its solubility can be influenced by pH. Through the application of the Law of Mass Action, the solubility of weakly acidic and basic drug substances can be predicted as a function of pH with a considerable degree of accuracy, using the following equations for the weakly acidic and basic drugs.

$$\text{Weak Acid} \qquad S_t = K_s\left(1 + \frac{K_a}{[H^+]}\right) \qquad \text{Weak Base} \qquad S_t = K_s\left(1 + \frac{[H^+]}{K_a}\right) \qquad (7)$$

There are many drug substances for which pH adjustment does not provide an appropriate means for effecting solution. Very weakly acidic or basic drugs may require a pH that could fall outside the accepted tolerable physiological range or may cause stability problems with formulation ingredients. For example, an experimental indole had an equilibrium solubility at pH 1.2 of approximately 50 mg/mL. However, when the pH of this system was increased to approximately 2.0, the solubility decreased to less than 0.1 mg/mL. In cases like this one, or with nonelectrolytes, it is necessary to use some other means of achieving better solubility.

Cosolvent systems have been used quite effectively to achieve solubility for poorly soluble drug substances under investigation. Propylene glycol, glycerin, sorbitol and polyethylene glycols have enjoyed a wide range of success in this area. They have been very useful and generally acceptable for improving solubility. Additional solvents such as glyceryl formal, glycofurol, ethyl carbonate, ethyl lactate and dimethylacetamide have been cited in a review article by Spiegel and Noseworthy;[8] however, it must be emphasized that with the possible exception of dimethylacetamide all of these solvents have not been used in oral products and their acceptability may be doubtful. The number of vehicles readily available to improve solubility is rather limited, yet the frequency of their use is rather high. Solubilizing a new drug substance can improve its availability. For example, when a triazinoindole was administered in a 0.02% solution it showed an equivalent response in antiviral activity to a 2.5% suspension. Information generated early in the preformulation stage can result in a refinement of the dosage regimen and allow for a more accurate estimation of the effective dose.

Cosolvents usually serve a twofold purpose in many pharmaceutical liquid products. They not only effect solution of the drug substance but also improve the solubility of flavoring constituents added to the product. Ideally, in determining the appropriate ratio of cosolvents to achieve the concentration one must achieve, it is recommended to effect solution at the concentration desired and then place the solution at and allow it to equilibrate. If precipitation occurs under these conditions, it may be necessary to alter the cosolvent ratio.

The use of surfactants of various types—nonionic, cationic or anionic—as solubilizing agents for medicinal substances is widespread (see Chapter 19 for illustrations of specific uses). The effect of Triton WR-1339 in solubilizing several steroids is shown in Fig 16.[9] The effect of an anionic, a cationic and a nonionic surfactant on the solubility of an antianginal compound being considered for clinical trials is shown in Fig 17. From such data investigators may be guided in the selection of solubilizing agents for use in preparations to be studied in humans, but it must be emphasized that the acceptability of a particular solubilizing agent depends also on other factors that determine its suitability for the intended use. For example, surfactants are known to interact with some preservatives and thereby decrease preservative action, for which reason the preformulation scientist should always recommend some type of biological test to demonstrate that the activity of the drug substance being studied is not reduced when it is solubilized by a surfactant.

Complexation phenomena sometimes can be used to impart better solubility characteristics. However, the degree of association and the extent to which solubility can be increased generally is not adequate for use in pharmaceutical products. In addition, many complexing agents have physiological activity. The most noteworthy example of the utility of complexation to enhance solubility is the PVP-iodine complex. Hydrotropy sometimes can be used to enhance solubility. High concentrations of urea, salicylates and xanthines have been used successfully on several occasions. Again, the concept is available but the increase in solubility normally observed is not adequate for use in pharmaceutical products.

Salt Formation

Salt-forming agents often are chosen empirically by the pharmaceutical chemist primarily on the basis of the cost of raw materials, ease of recrystallization and percentage yield. Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound in dosage forms. Furthermore, even when many

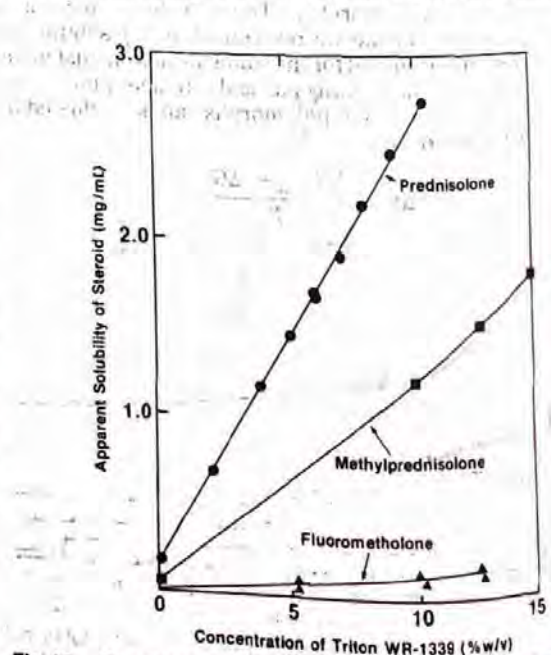

Fig 16. The effect of varying concentrations of Triton WR-1339 in water on the solubility of some anti-inflammatory steroids.[7]

Fig 17
33134

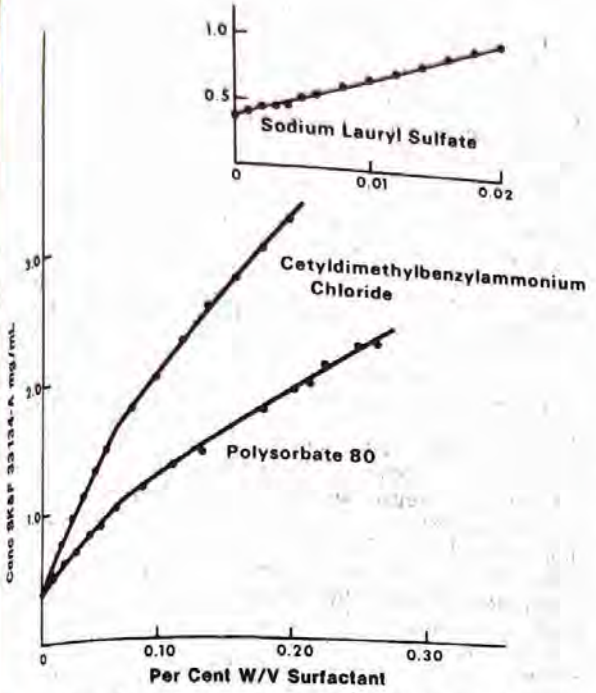

Fig 17. Effect of surfactant concentration on the solubility of SK&F 33134-A.

salts of the basic compound have been prepared, there are no effective screening techniques which make the selection process of the salt an easier task for the pharmacist. The fundamental considerations which may have some influence on salt selection are physical and chemical stability, hygroscopicity, flowability and solubility.

The number of salt forms available to the chemist is large. Table 2 lists the cations and anions present in FDA-approved commercially marketed salts of pharmaceutical agents.[10] The monoprotic hydrochlorides have been the most frequent choice of the available anionic salt-forming radicals, while sodium has been the most predominant cation. During preformulation evaluation it is extremely important to establish that the particular salt form in question will have properties that will result in a minimum of problems during the development of the dosage forms. Since toxicity studies usually are initiated soon after a compound has been designated for further studies in man, it is important that the salt form selected has been given a critical evaluation to determine whether or not its properties are suitable.

Since physical and chemical stability are vital to any pharmaceutical product, it is imperative that the preformulator evaluate both parameters. A systematic determination of the thermal stability, solution stability (at several pH's) and light-sensitivity of the drug substance provides essential input toward the selection of the most suitable derivative. Studies usually are initiated early to identify problems. Samples of the salts in question usually are placed under exaggerated conditions of heat and light in the presence and absence of moisture and subsequently analyzed to determine the amount of breakdown. In many instances stability-indicating analytical methods may not be available. In these cases it is necessary to resort to thin-layer chromatography to establish a qualitative assessment of stability. At the same time, samples are placed under high-humidity conditions and weighed periodically to determine the degree of hygroscopicity of the compounds. Compounds that have a tendency to adsorb or absorb moisture may present flowability problems during encapsulation.

Solubility characteristics also are evaluated. When a particular salt form has very good solubility (greater than 10%) it sometimes is difficult to prepare a suitable granulation using an aqueous granulating fluid, especially for high doses. Granulations prepared by these methods will not dry satisfactorily or the granulation will not flow uniformly from the hopper, resulting in a large weight variation during the compression stage. A critical evaluation of this type with different salt forms has been proven quite effective in enabling the preformulator to make the selection of the salt form of choice for further development.

Table 2—FDA-Approved Commercially Marketed Salts

Anion	Percent[a]	Anion	Percent[a]
Acetate	1.26	Iodide	2.02
Benzenesulfonate	0.25	Isethionate[c]	0.88
Benzoate	0.51	Lactate	0.76
Bicarbonate	0.13	Lactobionate	0.13
Bitartrate	0.63	Malate	0.13
Bromide	4.68	Maleate	3.03
Calcium edetate	0.25	Mandelate	0.38
Camsylate[b]	0.25	Mesylate	2.02
Carbonate	0.38	Methylbromide	0.76
Chloride	4.17	Methylnitrate	0.38
Citrate	3.03	Methylsulfate	0.88
Dihydrochloride	0.51	Mucate	0.13
Edetate	0.25	Napsylate	0.25
Edisylate[c]	0.38	Nitrate	0.64
Estolate[d]	0.13	Pamoate (Embonate)	1.01
Esylate[e]	0.13	Pantothenate	0.25
Fumarate	0.25	Phosphate/diphosphate	3.16
Gluceptate[f]	0.18	Polygalacturonate	0.13
Gluconate	0.51	Salicylate	0.88
Glutamate	0.25	Stearate	0.25
Glycollylarsanilate[g]	0.13	Subacetate	0.38
Hexylresorcinate	0.13	Succinate	0.38
Hydrabamine[h]	0.25	Sulfate	7.46
Hydrobromide	1.90	Tannate	0.88
Hydrochloride	42.98	Tartrate	3.54
Hydroxynaphthoate	0.25	Teoclate[i]	0.13
		Triethiodide	0.13

Cation	Percent[a]	Cation	Percent[a]
Organic:		Metallic:	
Benzathine[k]	0.66	Aluminum	0.66
Chloroprocaine	0.33	Calcium	10.49
Choline	0.33	Lithium	1.64
Diethanolamine	0.98	Magnesium	1.31
Ethylenediamine	0.66	Potassium	10.82
Meglumine[l]	2.29	Sodium	61.97
Procaine	0.66	Zinc	2.95

[a] Percent is based on total number of anionic or cationic salts in use through 1974. [b] Camphorsulfonate. [c] 1,2-Ethanedisulfonate. [d] Lauryl sulfate. [e] Ethanesulfonate. [f] Glucoheptonate. [g] *p*-Glycollamidophenylarsonate. [h] *N,N'*-Di(dehydroabietyl)ethylenediamine. [i] 2-Hydroxyethanesulfonate. [j] 8-Chlorotheophyllinate. [k] *N,N'*-Dibenzylethylenediamine. [l] *N*-Methylglucamine.

Compressibility and Compactibility

Tablets remain a preferred dosage form, and information obtained during preformulation studies on the ability of powdered drugs to be compressed and compacted can be a valuable aid to formulators. Compressibility and compactibility relate directly to tableting performance. Compressibility can be defined as the ability of a powder to decrease in volume under pressure, while compactibility can be defined as the ability of a powder to be compressed into a tablet of a certain strength or hardness. Even though powdered drugs usually are formulated with excipients to modify compression and compaction properties, the properties of the powdered drug alone may be the primary determinant of its ability to be manufactured into a tablet. Significant differences in compression and compaction behavior often can be observed in different lots of the same drug. For example, changes in

crystallization or milling procedures may produce differences in behavior.

Compression and compaction most often are evaluated by measuring the tensile strength and hardness of compacts. Tensile strength commonly is measured by diametral compression of round tablets, where the analysis of strength accounts for the dimensions of the tablet.[11] Transverse compression of square compacts between platens narrower than the compact is reported to provide more reproducible results on a wider variety of powders.

Hardness can be defined as the resistance of a solid to local permanent deformation. Deformation hardness tests usually are measured by static impression or dynamic methods. The static method involves the formation of a permanent indentation on a solid surface by a gradual and regularly increasing stress load. Hardness is determined by the load and size of the indentation and is expressed as force per unit area. In dynamic tests, the solid surface is exposed to an abrupt impact such as a swinging pendulum or an indenter allowed to fall under gravity onto the surface. Hardness then is determined from the rebound height of the pendulum or the volume of the resulting indentation.

Hiestand has used adaptations of a compression test and a hardness test to obtain measurements that are used to formulate three dimensionless parameters or indices.[12] The indices are used to characterize the relative tableting performance of individual components or mixtures. The *Strain Index* is the ratio of dynamic indentation hardness to reduced Young's modulus. The *Bonding Index* is the ratio of tensile strength to indentation hardness. The *Brittle Fracture Index* is obtained by comparing the tensile strengths of square compacts with and without a hole at their center. The indices themselves do not measure intrinsic properties of a chemical compound, but rather the traits that influence the tableting performance of a specific lot of chemical. It is necessary to know the magnitude of all three indices to predict the variety of tableting properties that may be incurred. Such information can act as a guide in selecting excipients to overcome problem properties of a drug ingredient.

Chemical Properties

The evaluation of the physical and chemical stability of a new drug substance is an important function of the preformulation group. The initial work should be designed to identify those factors that may result in an alteration of the drug substance under study. The physical pharmacist initially can anticipate the possible type of breakdown that a compound will be subjected to by examination of the chemical structure of the compound. For example, esters and amides are sensitive to hydrolytic degradation while acridanes and catecholamines are sensitive to oxidative degradation. With this preliminary knowledge one may more effectively design studies to identify the problems early. At this point the primary concern is not the pathway or mechanism of degradation. A stability-indicating method of analysis usually is not available early in the preformulation phase. Techniques such as thin-layer chromatography, diffuse reflectance and thermal analysis can be used to provide data to assess preliminary stability. Sometimes, the preliminary evaluation is complicated by the presence of impurities. It is essential that the drug under study be pure before any stability tests are undertaken. The presence of impurities can lead to erroneous conclusions in the preformulation evaluation.

Drug Substance Stability—It is extremely important to determine the stability of the bulk chemical as early as possible. One hardly would expect to prepare stable dosage forms with a chemical substance that was not stable in the pure state. Samples of the chemical are subjected usually to various conditions of light, heat and moisture in the presence and absence of oxygen. The chemical is placed in sealed vials with and without moisture and stored at various elevated temperatures which may vary to some degree from laboratory to laboratory. Light-sensitivity is measured by exposing the surface of the compound to light. Sunlamps are sometimes used to exaggerate light conditions. Hygroscopicity is evaluated by placing the chemical in open petri dishes at relative humidities from 30 to 100%. The samples are monitored regularly for physical changes, moisture pickup and chemical degradation.

Most drug substances are either stable at all conditions, stable under special conditions of handling, unstable without special handling or completely unstable. When drug substances are found to have some stability problems, it may be important to define the pathway of degradation and initiate studies to stabilize the compound with appropriate additives.

At this point, it may be advisable to consider some of the more prominent reactions accounting for instability of new drug substances. Obviously, some compounds will not undergo any appreciable decomposition if kept dry and away from air in a sealed container. It must always be assumed that the new drug substance is in some kind of formulation environment that may lead to instability problems.

Hydrolytic Degradation—Hydrolysis is probably the degradative process encountered most frequently in the formulation of new drugs. It is safe to assume that most new drugs will be exposed to water at some stage during processing or during storage; hence, hydrolysis may occur unless the conditions are optimum. Hydrolysis occurs with esters, amides, salts of weak acids and strong bases and thioesters, among others. A few drug compounds that undergo hydrolytic degradation are procaine, penicillin, aspirin and chlorothiazide.

From a kinetic standpoint, hydrolysis reactions are second-order reactions because the rate is proportional to the concentration of two reactants. However, in aqueous solutions since water is usually present in excess and at relatively constant concentration, the reactions are treated experimentally as monomolecular or first-order reactions. This simplification permits calculations of the extent of decomposition under precise experimental conditions by less-complicated means. Extrapolation of the exaggerated rates to room temperature makes it possible to establish more expeditiously shelf-life stability of potential new drug products.

The rate of hydrolysis can be affected by temperature and by hydrogen or hydroxyl ion concentration when the hydrolytic process is dependent on pH. Figure 18 shows the pseudo-first-order behavior as a function of pH for carbuterol in aqueous solution at constant ionic strength at 85°. The effect of temperature is illustrated in Fig 19 for carbuterol at pH 4.0 and 10.0 respectively.[13] For solids, the amount of moisture present is minimal. When considering a drug substance that undergoes hydrolytic degradation, studies are designed to establish the conditions of pH and buffer concentration where minimum decomposition occurs. There sometimes is a wide range of pH adjustment which a drug substance can tolerate, and then sometimes the range is narrow. For example, CI-988, a dipeptoid cholecystokinin-B receptor antagonist, was shown to have maximum stability between pH 6.0 and 6.5. The pH-rate stability profile

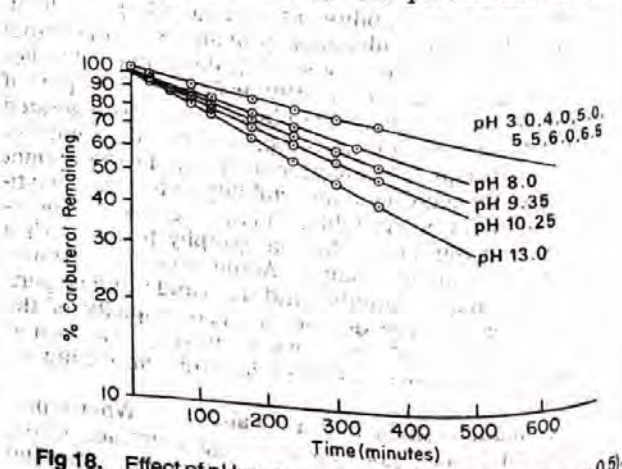

Fig 18. Effect of pH on carbuterol degradation at 85° ($\mu = 0.5$)

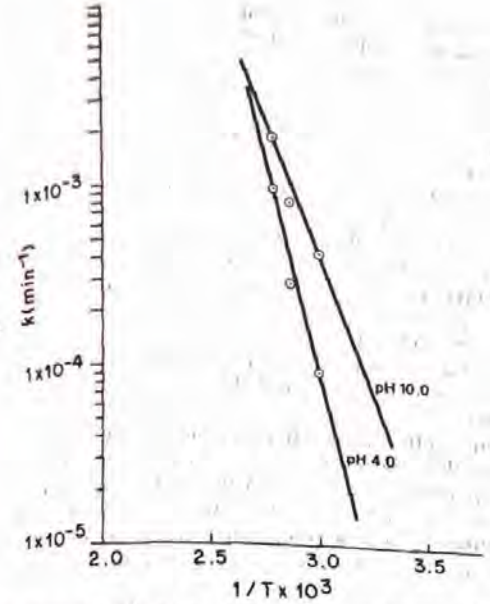

Fig 19. Typical Arrhenius-type plot depicting the temperature dependency of carbuterol hydrolysis at pH 4.0 and 10.0.

which was shown to be independent of salt form, is shown in Fig 20.[14] It is described by two reaction pathways: spontaneous or water-catalyzed degradation of the nonionized form and specific base-catalyzed degradation of the ionized form. A similar pH-rate stability profile, as shown in Fig 21, was found to occur for the lactamization of gabapentin.[15] In aqueous solution, gabapentin undergoes an intramolecular aminolysis to yield a stable, cyclized lactam product over the pH range of 1.4 to 11.1, with maximum stability occuring at pH 6.0. The buffer-independent pH-rate profile was described by two reaction pathways: a specific acid-catalyzed and specific base-catalyzed lactamization of the uncharged species. Another drug substance, carbuterol, hydrolyzed by an intramolecular process showed maximum stability over a wide pH range. Even though these compounds exhibited a wide range of pH for optimum stability in aqueous solution, they could not be formulated and provide products with satisfactory shelf lives without special cosolvent systems and/or special storage conditions. Buffering aqueous solutions to provide a pH for optimum stability can lead to stability problems. Stability sometimes is affected by buffer concentration; for example, carbuterol stability was shown to be affected by phosphate buffer concentration.

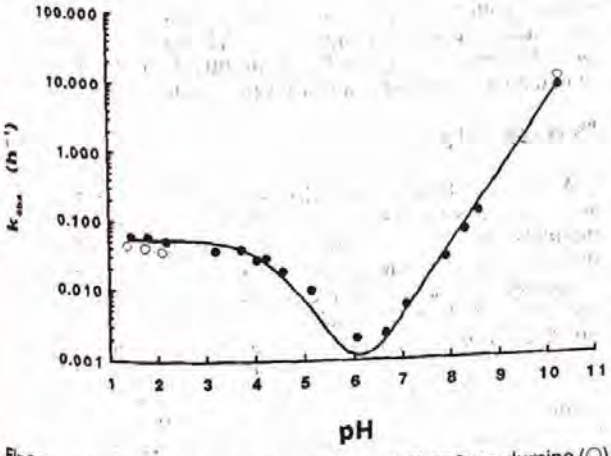

Fig 20. pH-rate profile for the degradation of CI-988 meglumine (○) and CI-988 sodium (●) at 80° and μ = 0.5*M* (with NaCl). The line represents the theoretical profile generated with nonlinear least-squares regression of the experimental data (●).

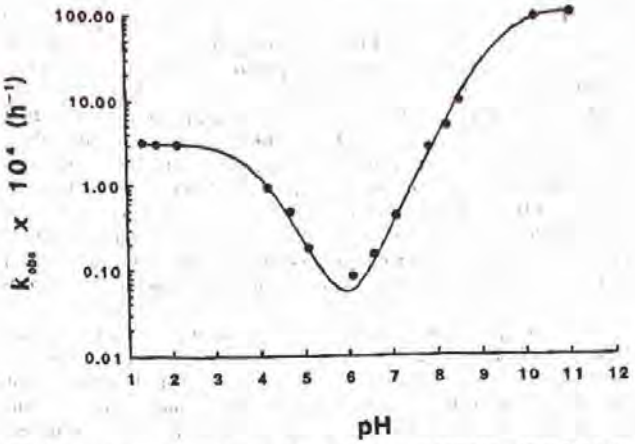

Fig 21. pH-rate profile for the lactamization of gabapentin at 80° and μ = 0.5*M* (with NaCl). The line represents the theoretical profile generated with nonlinear least-squares regression of the experimental data (●).

Another manner in which the preformulation scientist can overcome an instability due to hydrolysis is to recommend the preparation of an insoluble salt form or to prepare a solid dosage form. Insoluble chlorothiazide is stable in neutral aqueous suspensions, but solutions of the sodium salt at relatively high pH decompose rapidly. Frequently, the replacement of water by some other solvent, such as alcohol or the polyhydroxy solvents, reduces the hydrolytic rate of degradation for some systems. Acetylsalicylic acid suspensions containing high concentrations of sorbitol improved stability. Ampicillin also was shown to be more stable when the concentration of alcohol was increased. The formation of molecular complexes with aromatic esters greatly reduces the hydrolytic rate of degradation.

It also has been shown that stability of some compounds may vary depending on whether or not they exist in the micellar or nonmicellar state. For example, a difference in the chemical stability of penicillin exists in the micellar state from that in the monomeric state.

Oxidation—Oxidative degradation is as important as hydrolysis in the preliminary stability evaluation of new-drug substances. Studies should be initiated to establish the oxidative route, then steps should be taken to determine what additives can minimize the degradation. Oxidative degradation is common with many drug compounds. Ascorbic acid, epinephrine, vitamin A, chlorpromazine, isoproterenol, morphine, resorcinol and unsaturated fats and oils are subject to oxidative degradation. The oxidation reaction depends on several factors, including temperature, oxygen concentration in the liquid, impurities present and the concentration of the oxidizable component. The temperature effect in solutions is usually minimal; however, in the dry state it is more pronounced since other factors such as moisture dictate its stability behavior.

Initially, it is important to establish that oxidation is taking place. Solutions of the drug substance in question are exposed to various exaggerated conditions of light and oxygen tension in amber and flint-glass containers. Samples are analyzed for degradation. When it has been established that the oxidative route is the principal pathway for degradation, appropriate additives are used to determine what effect they might have on the stability. Sometimes pH is critical, since a great number of oxidation-reduction processes depend on the concentration of hydrogen or hydroxyl ions. Light usually accelerates degradation, thus the storage of products in dark containers does much to preserve stability. Photochemical changes many times involve the formation of other reactive

compounds or free radicals which function to propagate the decomposition, once started. Auto-oxidation may occur in the absence of light when susceptible materials, such as fats and oils, are stored in the presence of air. The auto-oxidation of phenolic compounds is of special significance since compounds such as epinephrine and isoproterenol degrade in this manner. Heavy metal ions, eg, cupric and ferric, accelerate the oxidation of ascorbic acid and the phenothiazines. Frequently, only trace quantities of these ions, occurring as impurities, may be sufficient to cause an increased rate of decomposition. This can be a consistent problem since many of the so-called inert ingredients may have heavy metal contaminants.

The oxygen concentration in solution is a factor in many cases and often depends upon the temperature of storage or the solvent employed. Oxygen is more soluble in water at lower temperatures so that oxygen-dependent reactions can sometimes proceed more rapidly at the lower temperatures. Ascorbic acid is more stable in 90% propylene glycol or in Syrup USP than in water, presumably because of the lower oxygen concentration in these vehicles. Oxidative degradation is an extremely complex process since the overall rate is dependent upon several factors. Preparations sensitive to oxidation are sometimes stabilized by effectively removing the oxygen and by the addition of suitable additives. Nitrogen flushing has been used successfully for this purpose. A wide variety of reducing agents and compounds to sequester metals and inhibit chain reactions has been employed for stabilization, but relatively few are acceptable for parenteral products. Often, it is necessary to combine ingredients and adjust pH to maximize stability. Detailed kinetic studies have been reported for the oxidative decomposition of prednisolone.

The physical pharmacist has a difficult task with oxidative degradation. Initially, experiments must be designed that will encompass many variables. Preparing samples at several concentrations containing antioxidants plus sequestering agents at several pH levels and placing them in flint or amber containers with and without nitrogen is a common procedure. The subsequent evaluation of these limited data is critical. Light-sensitivity studies with several formulations of prochlorperazine resulted in the selection of a stable formula. In a study with idoxuridine it was shown that placing the aqueous solution in an amber container was sufficient to protect the product from oxidative degradation.

Drug Substance–Excipient Interaction—Drug substance–excipient studies are designed to determine a list of excipients that can be used routinely in the final dosage forms. Lactose, sucrose, calcium sulfate, dicalcium phosphate, starch and magnesium stearate are some of the substances routinely tested in combinations. Some basic observations with the drug substance and/or its salt form sometimes can dictate what excipients can be used. For example, one would not consider using sucrose or lactose if the drug substance being considered is a primary amine. This system has the potential for interaction to form a colored compound readily detected by a color change.

Various means have been used for detecting potential interactions and incompatibilities. Diffuse reflectance techniques have been used to detect interactions. This has been done by comparing the spectra obtained initially with those obtained after storage at exaggerated conditions. A shift in absorption has been interpreted as an interaction. Thin-layer chromatography also has been used. When excipients are present it is usually advisable to set a mixture of the excipients at the same conditions as the excipient-drug mixtures. This will give a comparison of the chromatograms of both systems. If any new degradation products are present, the source may be determined more easily.

Mixtures containing at least two levels of drug concentration with excipients are sealed in vials containing 5% water. These vials are stored under exaggerated conditions of light and heat for various time periods. The resultant samples are observed physically and analyzed by an appropriate technique to get a qualitative determination. At this point in the stability evaluation, which is a preliminary screening process, it is not necessary to know exactly how much has degraded. It is an all-or-none effect. The search is for the excipients that have no effect on the stability of the active ingredient.

Even an excipient such as microcrystalline cellulose, often assumed to be chemically inert, can have physical interactions with a drug substance that can affect the performance and analytical testing of a formulated dosage form. CI-977, a centrally acting kappa-opioid agonist, was found to adsorb onto microcrystalline cellulose, croscarmellose and sodium starch glycolate.[16] The extent of adsorption was affected by pH, ionic strength and ionic species. Results showed that divalent cations, and to a lesser extent monovalent cations, inhibited adsorption by reducing both the affinity of the adsorbent for the adsorbate, and the adsorptive capacity of the adsorbent.

When solution interactions are being investigated and the incompatibilities are evident, it is wise to recommend an *in vivo* experiment to evaluate availability. On occasion, interaction may occur in solution that is not detectable with routine procedures. For example, clindamycin was found to interact with cyclamates, which interfere with the absorption of the drug.

Other Changes—Optically active substances may lose their optical activity; eg, through racemization. If the enantiomorphic compounds possess different degrees of physiologic action, such changes may result in reduced therapeutic effect. The FDA is constantly adopting stricter guidelines for the development of stereoisomeric drugs.[17,18] Even though stereoisomeric pairs essentially may have the same physical (except for optical rotation) and chemical (except in a chiral environment) properties, they are often readily distinguishable by biological systems. The development of racemic mixtures raises issues of acceptable manufacturing control of synthesis and impurities, adequate pharmacological and toxicological assessment, proper characterization of metabolism and distribution, and appropriate clinical evaluation. Hence, the interconversion from one isomer to another can lead to different pharmacokinetic properties (absorption, distribution, biotransformation and excretion) and quantitatively or qualitatively different pharmacological or toxicological effects. Epinephrine has been shown to undergo racemization under various acidic and basic conditions. Although the potential for this to become evident during a preformulation evaluation is rare, one should always be aware of this possibility. Polymerization is also a remote possibility. Darkening of glucose solution is attributed to polymerization of the breakdown product, 5-(hydroxymethyl)furfural. Isomerization, which is the process involving the change of one structure into another having the same empirical formula but with different properties in one or more respects, also can occur; again, the occurrence is rare. Deamination and decarboxylation can occur sometimes. This type of change would be detected easily since the resultant degradation products would have completely different properties.

Permeability

A preformulation evaluation should include studies to assess the passage of drug molecules across biological membranes. These membranes act as lipid barriers to most drugs and permit the absorption of lipid-soluble substances by passive diffusion. Lipid-insoluble substances can cross the barrier only with considerable difficulty. The pH-partition theory explains the interrelationship of the dissociation constant, lipid solubility, pH at the absorption site and the absorption characteristics of drugs across membranes. The theory has evolved following a series of investigations in laboratory animals and man and is the basis of much of the current understanding of absorption of drugs.

Data obtained from basic physical-chemical studies described earlier may give the preformulation scientist an indication of possible absorption difficulties. Experimental tech

niques are available that can be used to give a more accurate assessment of absorption problems. An *in vitro* system that has been used extensively consists of an aqueous/organic solvent/aqueous system which has the advantage of being simple, allows for accurate pH control, membrane thickness and other variables. It can be described mathematically in precise terms. However, the interpretation and correlation of data are limited when applied to biologic systems.

Another *in vitro* procedure, the everted sac technique, is a simple and reproducible method for determining the absorption characteristics of drugs. Isolated segments of rat small intestines are everted and filled with a solution of the drug being evaluated, and the passage of drug through the membrane is determined. This technique has been used to measure the permeability of a number of drug substances.[19] It also can evaluate both passive and active transport of drugs. The fact that the preparation has been removed from the animal and its normal blood supply is a distinct disadvantage.

The *in situ* technique developed by Doluisio, *et al*,[20] for the study of membrane permeability appears to overcome the disadvantages of the everted sac technique. Since the intestine is not removed from its blood supply, the results would be expected to be similar to those obtained in intact animals. A disadvantage of the technique is that the procedure does not account for the loss of fluid from the solution by absorption in the intestine. Nonabsorbable markers, such as phenol red, can be added to the drug solution to solve this problem.

The techniques described can give the preformulation scientist an indication of possible absorption problems or suggest that little or no difficulty will be observed in the passage of a particular drug product through the biological membranes. This information, along with eventual studies in man, serves to establish possible *in vitro / in vivo* correlation for dissolution and bioavailability. These data are important in establishing quality-control specifications for the products which will ensure consistent biological performance from subsequent lots.

Proteins and Peptides

Proteins and peptides produced by the commercialization of biotechnology are presenting preformulation scientists with new challenges. In general, protein and peptide drugs are more expensive to produce, more potent and more difficult to analyze than nonprotein and nonpeptide drugs. They frequently are formulated as parenterals instead of oral dosage forms because they are unable to be absorbed from the GI tract, unstable in GI fluids or subject to rapid first-pass metabolism. Degradation of proteins and peptides occurs not only by covalent bond reaction but also by denaturation. The prediction of shelf-life by the Arrhenius equation is usually not applicable.

Degradation by reaction of the covalent bond can be characterized by the following major reactions: hydrolysis, transpeptidation, racemization, oxidation, diketopiperazine formation, disulfide exchange and photodecomposition. Hydrolysis can occur at the peptide linkage (R-NH-CO-R), but it is more stable than the ester linkage (R-O-CO-R) unless cleavage is assisted by a neighboring group. Hence, peptides such as oxytocin and captopril are stable enough for liquid parenteral formulations. Transpeptidation occurs when amino acid residues cyclize back onto the peptide chain and the cyclic intermediate undergoes hydrolysis. Racemization can occur in acidic or alkaline medium, and if proline or glycine occur in the *N*-terminal position, diketopiperazine formation is facilitated. Cysteine, methionine and tryptophan are susceptible to oxidation, and since disulfide exchange is concentration-dependent, oligomers are formed frequently as a result of the creation of disulfide bonds between peptide chains. Photodecomposition of tryptophan residues may lead to discoloration and photoproducts of increased molecular weight.

Degradation via denaturation occurs when the conformational structure of a protein or peptide is altered. Potential factors that can denature a molecule include ionic strength, surface-active agents or processing conditions that subject the molecule to shear or adsorption. Identification of the preferred conformation, and mechanisms by which it can be altered, is critical in formulating the molecule as a stable drug. Hydrogen bonds act to stabilize conformational structure and the presence of water promotes hydrogen bonding. Hence, agents that disrupt the water-protein interaction such as salts and molecules with ionic side chains can promote conformational instability.

The increased size of the protein molecule, as compared to more traditional synthetic organic drug molecules, complicates traditional analytical methods and makes any one method itself inadequate to fully quantitate and characterize the protein. Consequently, an array of analytical methods is required and stability studies are a complex and time-consuming exercise. Usually, characterization of the protein requires probing each structural or functional feature of the molecule. Characterization assays may include amino acid sequence, isoelectric point, molecular size and glycosylation pattern. An electrophoretic technique, sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), is the most common technique for determination of molecular weight. Gel-permeation chromatography and ultracentrifugation also are used to determine molecular size and size distribution. HPLC chromatographic techniques, such as reversed-phase, ion-exchange and size-exclusion, are being used increasingly to quantitate proteins.

Several methods can be used to study denaturation of proteins. These include thermal analysis, determination of critical micelle concentration, determination of cloud-point, light scattering and fluorescence spectrometry. Thermal analysis with a scanning microcalorimeter is used to measure energies of transition in solution and is useful for determining the effect of stabilizing excipients on proteins in solution. Measurement of the critical micelle concentration also can be used as a tool to study the ability of an excipient to stabilize or disrupt the hydrophobic interactions which promote micellerization. Cloud-point measurements (the temperature, when cooled, at which a solution becomes cloudy) also have been suggested as a tool to study the effects of solvents or excipients on denaturation. Fluorescence spectrometry can be used to measure thermal denaturation by using a fluorescent probe whose fluorescence increases when a protein is denatured.

The ultimate analytical procedure for proteins is the bioassay that evaluates the desired biological activity. Even though bioassays determine the biological activity of the molecule, these tests usually show large assay variability. In addition, they are often unable to distinguish between two similarly acting proteins. Even so, regulatory agencies typically require a bioassay as part of any stability protocol.

Proteins and peptides can be stabilized in many ways, usually employing empirical, rather than theoretical, procedures. For parenteral formulations, excipients are added to enhance stability. Serum albumin, itself a relatively stable protein, is used commonly as a stabilizer for peptides and proteins. It may inhibit surface adsorption and act as a cryoprotectant during lyophilization. Amino acids, such as glutamic or aspartic acid, may chelate metals such as zinc, which may cause aggregation; however, metal ions, such as calcium, are essential to the stability of certain amylases and proteases. Phospholipids and fatty acids also are potential stabilizers. Even though surfactants have a high denaturing effect, they also may inhibit the effects of other denaturants.

Proteins, as opposed to nonprotein drugs, may find a dilute aqueous medium unfavorable. Therefore, one should attempt to create an environment similar to the natural habitat of the specific protein. This environment would be rich in proteins and carbohydrates, low in oxygen and have a high degree of immobilized water. However, as methodologies for studying denaturation and degradation become more defined, the number of excipients needed to stabilize a formulation can be limited selectively.

Formulation Ingredients

Although preliminary screening of commonly used excipients with new-drug substances has become routine in preformulation studies, there are occasions when problems arise because of the interaction with additives such as preservatives, stabilizers, dyes and, possibly, flavors. A discussion of some problems that have risen is in order to make formulators aware that they should be concerned about the potential for interaction whenever another ingredient is added to a formulation.

Preservatives—Each time a liquid or semisolid pharmaceutical dosage form is prepared, it is necessary to include a preservative in the formulation. Such preservatives as sodium benzoate, sorbic acid and the methyl and propyl esters of *p*-hydroxybenzoic acid (parabens) have been used in these systems for many years. There have been reports that the parabens have been inactivated when used in the presence of various surface-active agents and vegetable gums. This loss of activity might be due to the formation of complexes between the preservative and the surfactant. A dialysis technique has been used to demonstrate an interaction between polysorbate 80 and the parabens. This observation becomes critical if the level of preservative added is borderline with respect to the preservative-activity threshold. The desired preservative effect may not be achieved unless an excess of the preservative is added to compensate for that which is complexed. It also has been shown that molecular complexes form when the parabens are mixed with polyethylene glycol, methylcellulose, polyvinylpyrrolidone or gelatin. The degree of binding was less than that observed with polysorbate 80. Sorbic acid also interacts with polysorbates but does not interact with polyethylene glycols. The quaternary ammonium compounds also are bound by polysorbate 80 to reduce their preservative activity. Benzyl alcohol also was shown to be adsorbed by certain types of rubber stoppers. Subsequent work has shown that butyl rubber does not interact with benzyl alcohol.

Antioxidants—During the preformulation evaluation of compounds that are sensitive to oxidation often it is commonplace to test several levels of antioxidant concentrations added to aqueous systems in order to determine the relative effectiveness of the antioxidants. Sodium bisulfite and ascorbic acid are two antioxidants that are used widely in pharmaceutical systems. Sodium bisulfite yields a colorless water-soluble salt when it is oxidized. It will add to double bonds, react with aldehydes and certain ketones and contributes in bisulfite cleavage reactions. Many of the reactions with bisulfite are irreversible, and the resulting sulfonic acids frequently are biologically inactive. Epinephrine has been shown to interact with bisulfite to form a bisulfite addition product. Other sympathomimetic drugs, principally the *ortho-* or *para*-hydroxybenzyl alcohol derivatives, also react with bisulfite in a similar manner. The *meta*-hydroxy alcohol does not react. Sometimes these interactions are reversible as in the case with the adrenocorticosteroid molecules.

Ascorbic acid, on the other hand, is less reactive. However, when mixed with compounds having a primary amine nucleus, there is the tendency for interaction to form a highly colored Schiff base. One must be aware of this possibility when selecting a suitable antioxidant.

Suspending Agents—Occasionally, it will be necessary to consider the use of a suspending agent to prepare some preliminary suspension preparations for stability evaluation prior to starting toxicity testing. The physical pharmacist should be aware of the potential for these additives to react with the drug substance being evaluated. Anionic water-soluble compounds, such as sodium carboxymethylcellulose, alginic acid, carrageenin and other hydrocolloids, although generally considered inert, frequently interact with drug compounds in solution. Carboxymethylcellulose and carrageenin form complexes, or possibly salts, with many medicinal agents including procaine, chlorpromazine, benadryl, quinine, chloropheniramine, neomycin and kanamycin. In some instances the formation of the complex imparted better stability to the system. When this problem is suspected, it is important to conduct appropriate tests to insure that an interaction does not take place in the system being evaluated.

Dyes—Although preformulation tests usually are conducted long before any consideration of coloring the intended dosage forms, they should not be overlooked. Dyes are chemical in nature and contain reactive sites capable of causing incompatibilities. Several studies have demonstrated that certified dyes do react with drug substances. Sugars, such as dextrose, lactose and sucrose, were found to increase the rate of fading of FD&C Blue #2. Insoluble complexes also were formed when quaternary ammonium compounds were formulated with FD&C Blue #1.

Summary

The preformulation evaluation of new-drug substances has become an integral part of the development process. A thorough understanding of the physical-chemical properties of the new-drug substance under study provides the development pharmacist with data that are essential in designing stable and efficacious dosage forms. Many of the problems discussed and the solutions offered in this chapter resulted from application of scientific training of present-day pharmaceutical scientists. Their diverse skills, creative aptitudes and initiative provide the pharmaceutical industry with the essential ingredients to develop drug products that help maintain the health-care process at its highest level of excellence.

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