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CHAPTER 90

Oral Solid Dosage Forms

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Drug substances are most frequently 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 may also be included in the formulations to enhance the physical appearance, improve stability, and aid in disintegration after administration. These supposedly inert ingredients, as well as the production methods employed, have been shown in some cases to influence the release of the drug substances.[1] Therefore care must be taken in the selection and evaluation of additives and preparation methods to ensure that the physiological availability 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 physical 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, variations among dosage units of a given batch, as well as batch-to-batch differences, are 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 has greatly 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, validated processes and equipment, packaging, and the controls used during and after preparation (Fig 90-1).

Fig 90-1. 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 first used 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 continually being made to understand more clearly the physical characteristics of tablet compression and the factors affecting the availability of the drug substance from the dosage form after oral administration. Compression equipment continues to improve both as to production speed and the uniformity of tablets compressed. Recent advances in tablet technology have been reviewed.[2-5]

Although tablets are more frequently 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 are usually 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, 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 can also 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 widely used in the design of prolonged-action dosage forms.

Controlled-Release Tablets—Compressed tablets can be formulated to release the drug substance in a manner to provide medication over a period of time. There are a number of types which include delayed-action tablets in which the release of the drug substance is prevented for an interval of time after administration or until certain physiological conditions exist; repeat action tablets which periodically release a complete dose of the drug substance to the gastrointestinal fluids; and the extended release or sustained release tablets which continuously release increments of the contained drug substance to the gastrointestinal fluids. These tablets are discussed in Chapter 92.

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 contain sodium bicarbonate and an organic acid such as tartaric or citric. 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 t 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 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. 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 readily absorbed by this form of administration.

Molded Tablets or Tablet Triturates (TT)

Tablet triturates are usually made from moist material using a triturate 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 were originally 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 have ever 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. 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 90-2. The tablet is formed by pressure applied on the punches and is subsequently 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 an 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 readily ejected from the punch faces, the material must have a degree of lubrication to minimize friction and to allow for the removal of the compressed tablets.

Fig 90-2. Basic mechanical unit for tablet compression: lower punch, die, and upper punch (courtesy, Vector/Colton).

There are three general methods of tablet preparation: (1) the wet-granulation method; (2) the dry-granulation method; and (3) direct 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 are also influenced both by the method of preparation and by the added materials present in the formulation. In the preparation of compressed tablets the formulator must also 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 more easily broken, 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.[6,7] See Chapters 38, 76, and 77.

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 (1) diluents, (2) binders, and (3) 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 (1) disintegrants, (2) colors, and in the case of chewable tablets, (3) flavors, and (4) sweetening agents.

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 program is called the Codex of Pharmaceutical Excipient Project and the Academy's Industrial Pharmaceutical Technology Section has undertaken its organization and implementation.

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. Compressed tablets of dexamethasone contain 0.75 mg steroid per tablet, hence it is obvious that another material must be added to make tableting possible. Diluents used for this purpose include dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such tablets are commonly 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*, p 1613.

Most tablet formulators 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 diluent with the drug must be considered. For example, 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 to the point where they are not completely available 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) is usually used as an excipient in direct compression formulas. However, its presence in 5-15% concentrations in wet granulations has been shown to be beneficial in the granulation and drying processes in minimizing case-hardening of the tablets and in reducing tablet mottling.

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. 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. Since powders differ with respect to the ease with which they can be wetted, it is preferable to incorporate the binding agent in solution. By this technique it is often possible to gain effective binding with a lower concentration of binder. It should be noted that there are several "pregelatinized" starches available which are intended to be added in the dry form so that water alone can be used as the granulating solution.

The direct compression method for preparing tablets (see page 1613) 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 polyvinyl

pyrrolidone. 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 widely used as a binder. The concentration may vary from 10 to 20%. It is usually prepared as it is to be used by dispersing corn starch in sufficient cold purified water to make a 10% *w/w* solution and warming in a water bath with continuous stirring until a translucent paste forms.

Gelatin Solution Gelatin is generally used as a 10 20% solution; gelatin solutions should be freshly prepared 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 is then warmed in 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.

Glucose Solution—Generally a 25 50% solution is used Glucose does not dry out well and is therefore not suitable where the tablets are subject to humid conditions. These solutions are not true 25 and 50% solutions since the corn syrup contains only approximately 80% solids. To prepare the binder solution, the corn syrup is weighed and dissolved in purified water. Sufficient purified water is added to give the concentration desired on a weight basis. If clarification is desirable, it can be strained through cloth.

Ethylcellulose—This is insoluble in water. It is used effectively as a binder when dissolved in alcohol, or as a dry binder in a granulation which is then wetted with alcohol. As a binder in solution it is usually used as a 5% solution. It is widely used as a binder for moisture-sensitive materials. To make the solution, ethylcellulose is dissolved in anhydrous denatured alcohol and made up to the final volume on a weight basis.

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

It will be noted that binder solutions are usually 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.

Lubricants

Lubricants have a number of functions in tablet manufacture. They prevent adhesion of the tablet material to the surface of the dies and punches, reduce interparticle friction, facilitate the ejection of the tablets from the die cavity, and may improve the rate of flow of the tablet granulation. Commonly used lubricants include talc, magnesium stearate, calcium stearate, stearic acid, and hydrogenated vegetable oils. 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 dissolution of the drug substance.

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

Prolonged blending of lubricant with a granulation can materially 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 iuvestigated 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 is sometimes 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 yet been established.

Glidants

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

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 relensed from the tablet matrix as efficiently as possible to allow for its rapid dissolution. Materials serving as disintegrants have been chemically classified as starches, clays, celluloses, algins, gums, and crosslinked 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 new group of materials known as "super disintegrants" have recently gained in popularity as disintegrating agents. The name comes from the low levels (2–4%) at which they are completely effective. Croscarmelose, Crospovidone, and sodium starch glycolate represent examples of a crosslinked cellulose, a crosslinked polymer, and a modified starch molecule, respectively.

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. 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 is usually 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 the tablet down 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 the 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 the result a number of colorants have been delisted and several added. The colorants currently approved in the US include the following: FD&C Red No 3, FD&C Red No 40, FD&C Yellow No 5, FD&C Yellow No 6, FD&C Blue No 1, FD&C Blue No 2, FD&C Green No 3, a limited number of D&C colorants, and the iron oxides. Each country has its own list of approved colorants and formulators must consider this in designing products for the international market.

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 form of speckling to compressed tablets. The dyes available do not meet all the criteria required for the ideal pharmaceutical colorants. The photosensitivity of several of the commonly used colorants and their lakes has been investigated, as well as the protection afforded by a number of glasses used in packaging tablets. Another approach for improving the photostability of dyes has been in the use of ultraviolet-absorbing chemicals in the tablet formulations with the dyes. The Di-Pac line (*Amstar*) is a series of commercially available colored, direct compression sugars.

The most common method of adding color to a tablet formulation is to dissolve the dye in the binding solution prior to the granulating process. Another approach is to adsorb the dye on starch or calcium sulfate from its aqueous solution; the resultant powder is dried and blended with the other ingredients. If the insoluble lakes are used, they may be blended with the other dry ingredients. Frequently during drying, colors in wet granulations migrate, resulting in an uneven distribution of the color in the granulation. After compression the tablets will have a mottled appearance due to the uneven distribution of the color. Migration of colors may be reduced by drying the granulation slowly at low temperatures and stirring the granulation while it is drying. The affinity of several water-soluble anionic certified dyes for natural starches has been demonstrated; in these cases this affinity should aid in preventing color migration. Other additives have been shown to act as dye migration inhibitors. Tragacanth (1%), acacia (3%), attapulgite (5%), and talc (7%) were effective in inhibiting the migration of FD&C Blue No 1 in lactose. In using dye lakes the problem of color migration is avoided since the lakes are insoluble. Prevention of mottling can be helped also by the use of lubricants and other additives 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 widely used. With the banning of the cyclamates and the indefinite status of saccharin new natural sweeteners are being sought. Aspartame (*Searle*), recently made available, may

have 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 markedly affect the physical characteristics of the tablet granulation.

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 90-16 and 90-17). 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. A commonly used 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 second and third fingers and using the thumb as the fulcrum, yet doesn't break when it falls on the floor. For 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-thirties by the Monsanto Chemical Co. It is now distributed by the Stokes Div (*Pennwalt Corp*) 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, 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.

Fig 90-3. The Schleuniger or Heberlein tablet hardness tester shown with calibration blocks (courtesy, Vector).

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 1.4–1.7 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 the Vector Corporation. 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 90-3.

Hardness 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 tablet *friability*, and the measurement is made by use of the Roche friabilator. Rather than a measure of the force required to crush a tablet, the instrument is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling, and shipping. A number of tablets are weighed and placed in the tumbling apparatus where they are exposed to rolling and repeated shocks resulting from freefalls within the apparatus. After a given number of rotations the tablets are weighed and the loss in weight indicates the ability of the tablets to withstand this type of wear (Fig 90-4).

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. 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 carefully controlled. Thickness can vary with no 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

Fig 90-4. The Roche friabilator (courtesy, Hoffmann-LaRoche).

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 then 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. 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 generally recognized 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 given set of conditions for a group of tablets to disintegrate into particles. In the present disintegration test the particles are those which will pass through a 10-mesh screen. In 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 90-5. 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.

Fig 90-5. Vanderkamp Tablet Disintegration Tester (courtesy, Van-Kel).

Tablets are placed in each of the six cylinders along with a plastic disk 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 disks 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 min 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 min. For the exact conditions of the test, consult the USP.

Dissolution Test

For certain tablets the monographs direct compliance with limits on dissolution rather than disintegration. Since drug absorption and physiological availability depend on having the drug substance in the dissolved state, suitable dissolution characteristics are an important property of a satisfactory tablet. Like the disintegration test, the dissolution test for measuring the amount of time required for a given percentage of the drug substance in a tablet to go into solution under a specified set of conditions is an *in vitro* test. It is intended to provide a step towards the evaluation of the physiological availability of the drug substance, but as currently described 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 35 for a complete discussion of dissolution testing.

Validation

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

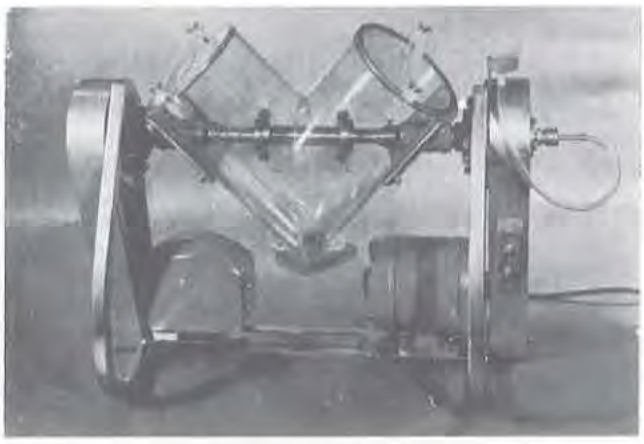


Fig 90-6. Twin-shell blender for solids or liquid–solids blending (courtesy, Patterson-Kelley).

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 (1) that the validation activity must begin in R&D and continue through product introduction; (2) that documentation is the key; and (3) that, in general, three batches represent an adequate sample for validation. Until the practice of validation for new products is firmly and universally adopted, retrospective validation (using historical data) for older products is a satisfactory approach.

Methods of Preparation

Wet-Granulation Method

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 the large scale. The steps in the wet method are (1) weighing, (2) mixing, (3) granulation, (4) screening the damp mass, (5) drying, (6) dry screening, (7) lubrication, and (8) 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 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 should always 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 deleteriously affected 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 means of precision blending and mixing in short periods of time (Fig 90-6). 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 90-7). On a large scale, ribbon blenders are also frequently employed and may be adapted for continuous production procedures. Mass mixers of the sigma-blade type have been widely used in the pharmaceutical industry.

Rapidly increasing in popularity are the high-speed, high-shear mixers such as the Lodige/Littleford, the Diosna, the Fielder, and the Baker-Perkins. For these mixers a full range of sizes are available. Fluid-bed granulation (discussed below) is also gaining wide acceptance in the industry. For both of these types of processing, slight modifications to the following procedures are required.

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,

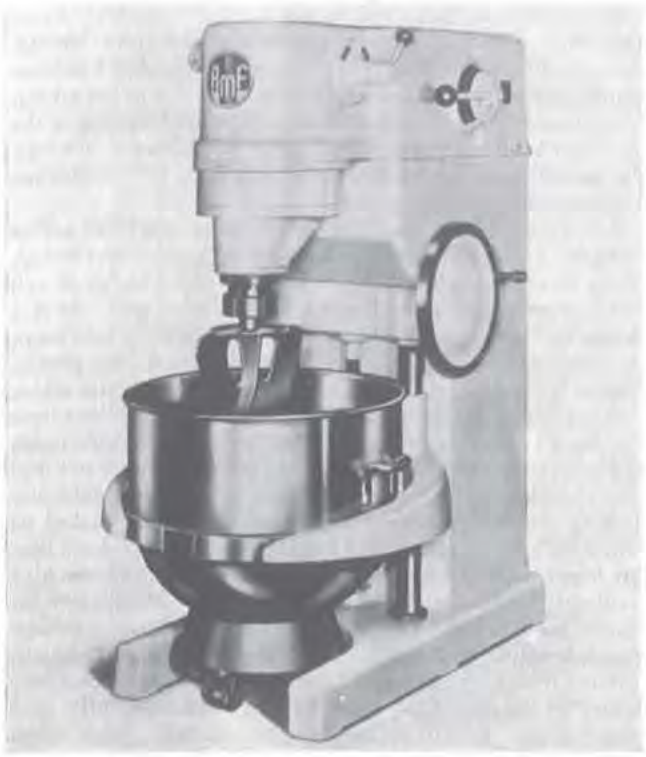


Fig 90-7. The Glen powder mixer (courtesy, Am Machine).

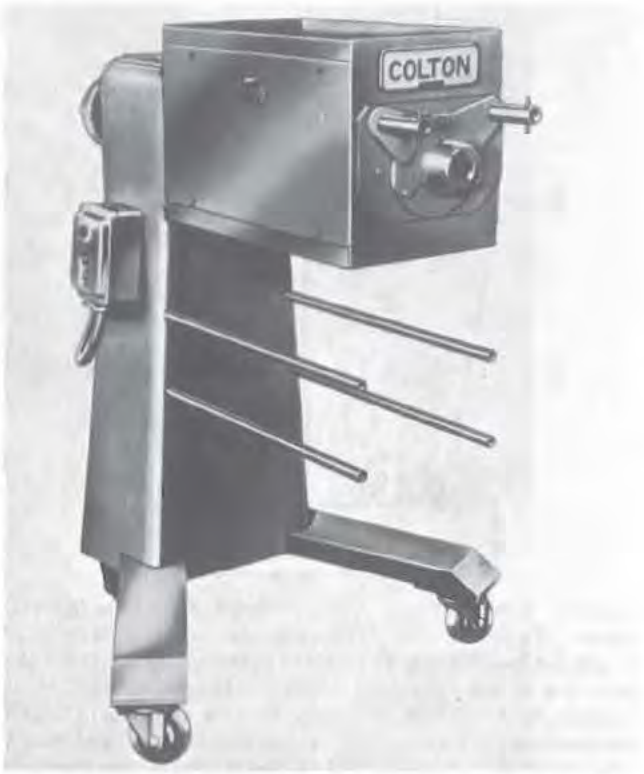


Fig 90-8. Rotary granulator and sifter (courtesy, Vector/Colton).

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, the Colton rotary granulator, the Fitzpatrick comminuting mill, or the Stokes tornado mill. See Fig 90-8. 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 is gradually forced through a perforated screen forming threads of the wet granulation. The granulation is then 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 90-9. While tray drying was the most widely used method of drying tablet granulations until recently, fluid-bed drying is now equally popular. Notable among the newer methods being introduced are the fluid-bed dryers. In drying tablet granulation by fluidization the material is suspended and agitated in a warm air stream while the granulation is maintained in motion. Drying tests comparing the fluidized bed and a tray dryer for a number of tablet granulations indicated that the former was 15 times faster than the conventional method of tray drying. In addition to the decreased drying time the fluidization method is claimed to have other advantages such as better control of drying temperatures, decreased handling costs, and the opportunity to blend lubricants and other materials into the dry granulation directly in the fluidized bed. See Fig 90-10.

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

In drying granulations it is desirable to maintain a residual amount of moisture in the granulation. This is necessary to

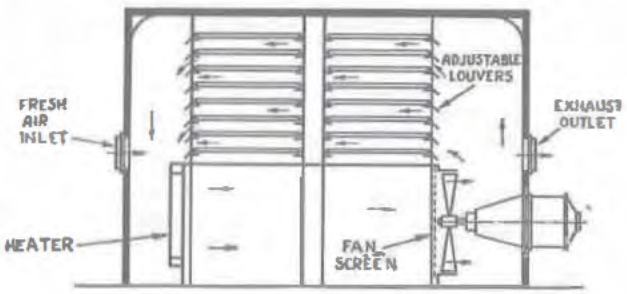


Fig 90-9. Cross section of tray dryer.

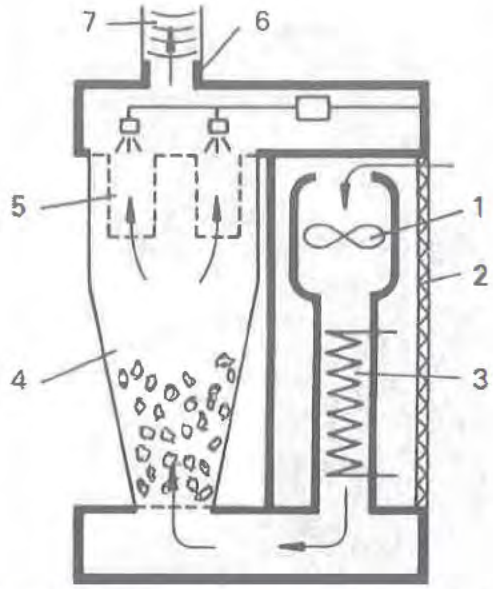


Fig 90-10. Fluid Bed Dryer. This equipment functions in the following manner. The moist product—either granulated or in powder form—is brought to a fluidized state by means of an upward hot air stream and carefully dried until the desired moisture content is reached. The air necessary for this process is obtained from the work area by means of an extractor fan (1), cleaned in the coarse dust filter (2) and heated to the desired temperature in the air heater (3). The air, thus prepared, now flows upward through the material in the product container (4) soaking up the moisture in the shortest period of time. The filter (5) retains the dust, which is periodically blown off during the process by compressed air. The exhaust air escapes into the open air through the socket (6) and the tube (7) (courtesy, Aeromatic).

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 an 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 $^{3}/_{16}$ in diam, use 20-mesh
Tablets $^{7}/_{32}$ in to $^{5}/_{16}$ in, use 16-mesh
Tablets $^{11}/_{32}$ in to $^{13}/_{32}$ in, use 14-mesh
Tablets $^{7}/_{16}$ in 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 is usually 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 tumbling action. Gentle action is desired to maintain the uniform granule size resulting from the dry-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. Air trapped in the tablets by the fine powder causes them to split apart after ejection from the machine. Fines, however, at a level of 10–20% are traditionally sought by the tablet formulator. The presence of some fines is necessary for the proper filling of the die cavity. Recently, even higher concentrations of fines were successfully used in tablet manufacture. Some investigators maintain 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.

Another approach toward the faster preparation of tablet granulations has come from the utilization of the air-suspension technique developed by Wurster.[8] Both Aeromatic and Glatt fluid-bed granulating equipment are available in a full range of sizes, from laboratory models to the largest production sizes. 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 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 can provide the same advantage. 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 (see page 1627). 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.[9]

In the Merck Sharp & Dohme facility at Elkton, Virginia, 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 facility represents an innovation in pharmaceutical manufacturing. See Fig 90-11.

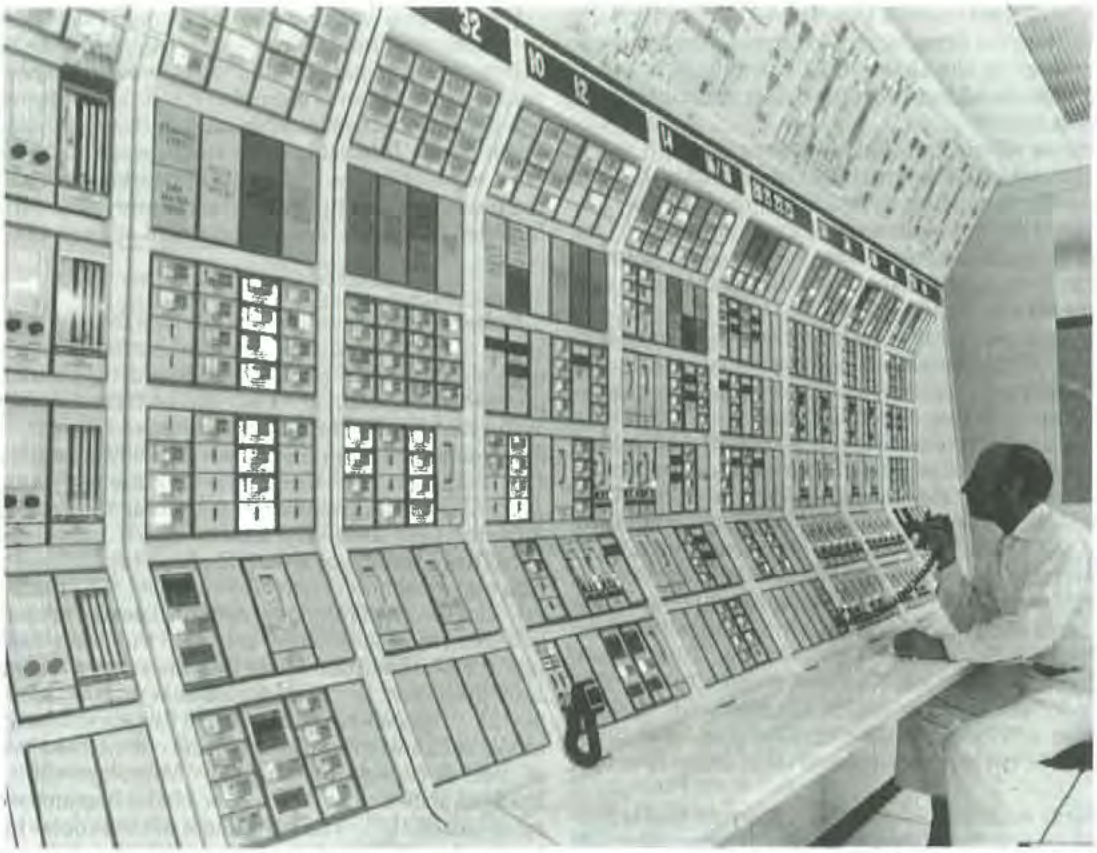


Fig 90-11. Computer control room for the first large-scale computer-controlled tablet manufacturing facility (courtesy, MSD).

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, a compressing, or a 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 Method

When tablet ingredients are sensitive to moisture or are unable to withstand elevated temperatures during drying, and when the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form granules. This method is referred to as dry granulation, precompression, or the double-compression method. It eliminates a number of steps but still includes (1) weighing, (2) mixing, (3) slugging, (4) dry screening, (5) lubrication, and (6) 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 are also 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 is constantly making efforts to increase the efficiency of tableting operations and to reduce costs by utilizing 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.[10]

Direct-compression vehicles or carriers must have good flow and compressible characteristics. These properties are imparted to them by a preprocessing step such as wet granulation, slugging, spray drying, spheronization, or crystallization. These vehicles include processed forms of most of the common diluents including dicalcium phosphate dihydrate, tricalcium phosphate, calcium sulfate, anhydrous lactose, spray-dried lactose, pregelatinized starch, compressible sugar, mannitol, and microcrystalline cellulose. These commercially available direct compression vehicles may contain small quantities of other ingredients (eg, starch) as processing aids. Dicalcium phosphate dihydrate (*Di-Tab*, Stauffer) in its unmilled form has good flow properties and compressibility. It is a white crystalline agglomerate insoluble in water and alcohol. The chemical is odorless, tasteless, and nonhygroscopic. Since it has no inherent lubricating or disintegrating properties, other additives must be present to prepare a satisfactory formulation.

Compressible sugar consists mainly of sucrose that is processed to have properties suitable for direct compression. It may also 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 widely used for chewable vitamin tablets because of its natural sweetness. One commercial source is *Di-Pac* (Amstar) prepared by the co-crystallization 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 mouthfeel 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 Corp.). 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 μm 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. They attempt to minimize air entrapment and consequently capping in the finished tablet. By increasing the density of the powder, higher uniformity in tablet weights is obtained. See Fig 90-24.

The gradual improvement of formulation additives and development of mechanical feeding devices for the high-speed rotary tableting machines indicate the acceptance of direct compression as the preferred method for the future. Of all the methods, direct compression is the most adaptable to automation. Interest in direct compression is also 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 1622.

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 cohesiven s for tableting. Spheronization equipment such as the Marumerizer (*Luwa Corp*) and the CF-Granulator (*Vector*) is commercially available. A wet granulation containing the drug substance, diluent (if required) and binder, is first passed 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 90-12). The pellets are then dried by conventional methods, mixed with suitable lubricants, and compr sed into tablets, or used as capsule-fill material. Microcrystalline cellulose has been shown to be an effective binder in granulations to be spheronized.[11,12] 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 can also 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.

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 90-13, the feed is sprayed into a current of warm filtered air. The air supplies the heat

Fig 90-12. The inside of a QJ-400 Marumerizer (courtesy, Luwa).

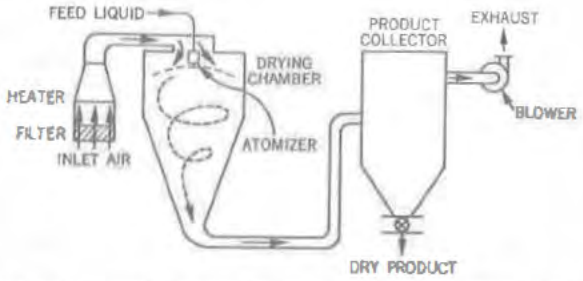


Fig 90-13. Typical spray-drying system (courtesy, Bowen Eng).

for 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 is then 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.[13]

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 at Lederle Laboratories using a salt precipitation process, followed by a freeze-drying. By utilizing 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 widely used in antacid preparations.

Encapsulation of chemicals can also 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 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 90-14 and 90-15. While round tablets are more generally used, 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: $^{3}/_{16}$ in, $^{7}/_{32}$ in, $^{1}/_{4}$ in, $^{9}/_{32}$ in, $^{5}/_{16}$ in, $^{11}/_{32}$ in, $^{7}/_{16}$ in, $^{1}/_{2}$ in, $^{9}/_{16}$ in, $^{5}/_{8}$ in, $^{11}/_{16}$ in, and $^{3}/_{4}$ in. Punch faces with ridges are used for compressed tablets scored for breaking into halves or fourths, although it has been indicated that variation among tablet halves is significantly greater than among intact tablets. However, a patented formulation[14] 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 Fig 90-16 and Fig 90-17. The use of the tablet sometimes determines its shape; effervescent tablets are usually large, round, and flat, while vitamin tablets are frequently 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.[15]

Regardless of the size of the tableting operation, the at-

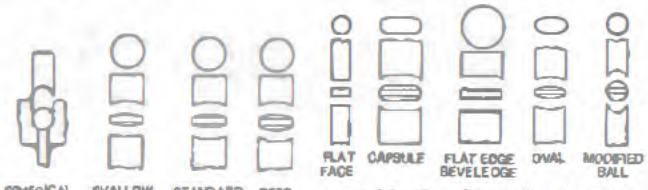


Fig 90-14. Concave punches.

Fig 90-15. Specially shaped punches.

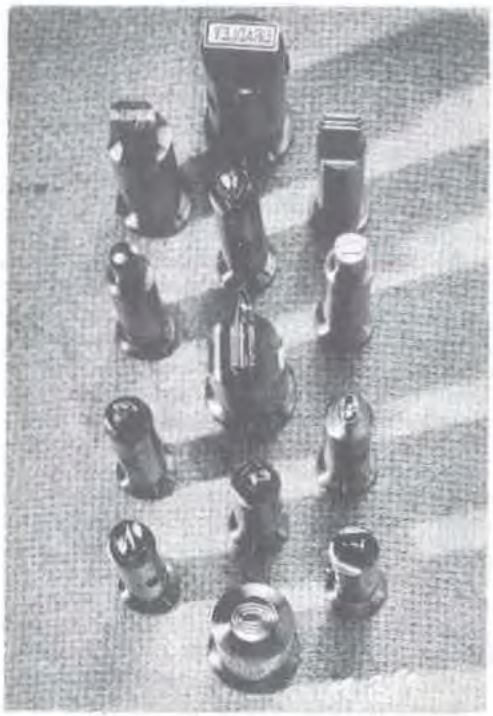


Fig 90-16. Collection of punches (courtesy, Stokes/Pennwalt).

tention 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 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.

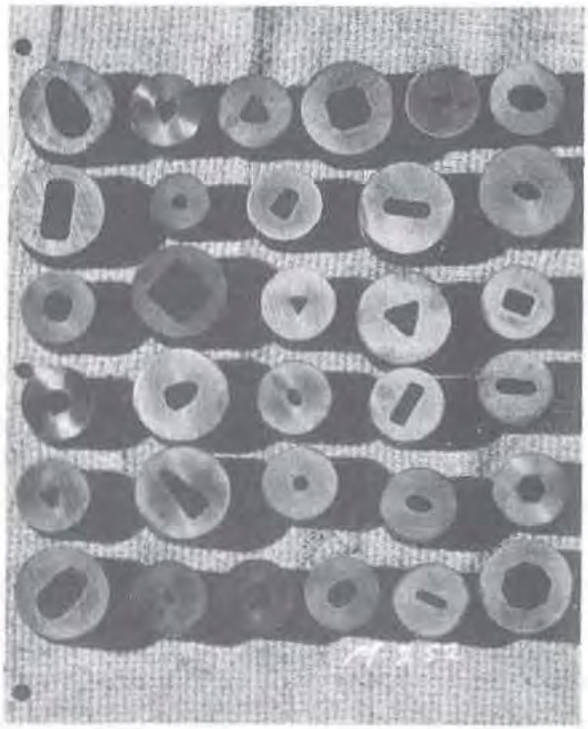


Fig 90-17. Collection of dies (courtesy, Stokes/Pennwalt).

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 I. 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 90-18. 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 in, sturdier models are required. This is also true for tablets requiring a high degree of hardness as in the case of compressed lozenges. The heavier models are capable of much higher pressures and are suitable for slugging.

Operation of Single-Punch Machines

In installing punches and dies in a single-punch machine insert the lower punch first by lining up the notched groove on the punch with the lower punch setscrew and slipping it into the smaller bore in the die table, the setscrew is not tightened 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 securely seated, 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 adjustments

Table I—Single-Punch Tablet Machines

Machine model	Maximum tablet diameter (in)	Press speed (tablets/min)	Depth of fill (in)
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	13/16
Model 35T[a]	3	36	2¼

[a] Widely used for veterinary boluses.

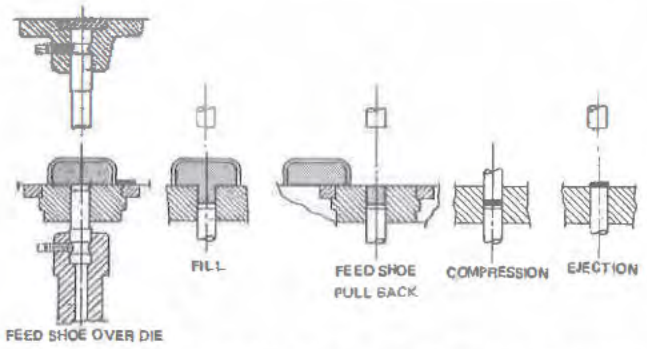


Fig 90-18. Formation of tablet on single-punch machine (courtesy, Vector/Colton).

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 15–30 min intervals.

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

As tablets are ejected from the machine after compression, they are usually 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

Fig 90-19. Model 747 High Speed Press, double-sided rotary compacting press designed to produce at speeds over 10,000/min (courtesy, Stokes/Pennwalt).

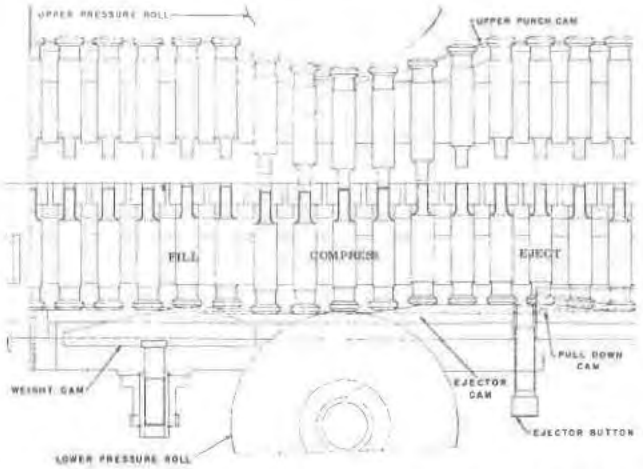


Fig 90-20. Tooling for a 16-station rotary press showing positions of the cycle required to produce 1 tablet/set of tooling (courtesy, Vector/Colton).

weight for the tablet. Compression takes place as the upper and lower punches pass between a pair of rollers. This action produces a slow squeezing effect on the material in the die cavity from the top and bottom and so gives a chance for the entrapped air to escape. The lower punch lifts up and ejects the tablet. Adjustments for tablet weight and hardness can be made without the use of tools while the machine is in operation. Fig 90-20 shows the tooling in a 16-station rotary press in the positions of a complete cycle to produce 1 tablet/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 readily removed for inspection, cleaning, and for inserting different sets to produce a great variety of sizes and shapes. 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 II.

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

Table II—Rotary Tablet Machines

Machine model	Tool sets	Maximum tablet diameter (in)	Press speed (tablets/min)	Depth of fill (in)
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
	42	7/8	750	2 3/4
Stokes-Pennwalt equipment				
512-1	16	5/8	350 1050	11/16
516-1	23	1 3/16	240–720	1 3/8
550-2	16	15/16	365 640	1 1/16
555	45	7/16	1050 4200	11/16
	35	5/8	800–3200	11/16
328-1	45	3/4	1600 4500	11/16
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

Table III—High-Speed Rotary Tablet Machines

Machine model	Tool sets	Maximum tablet diameter (in)	Press speed (tablets/min)	Depth of fill(in)
Vector Colton equipment				
2247	33	5/8	3480	3/4
	41	7/16	4300	3/4
	49	7/16	5150	3/4
Magna	66	23/32	10,560	3/4
	74	1/2	11,840	3/4
	90	7/16	14,400	3/4
Stokes-Pennwalt equipment				
555-2	35	5/8	800–3200	11/16
328-4	45	3/4	1600–1500	1 3/8
610	65	7/16	3500–10,000	11/16
747	65	7/16	3000–10,000	11/16
	53	5/8	2900–8100	11/16
	41	15/16	2150–6150	11/16
	Direct Triple Compression Type			
580-1	45	7/16	525–2100	11/16
580-2	35	5/8	400–1600	11/16
610	65	7/16	3500–10,000	13/16
	53	5/8	2900–8100	11/16
Manesty equipment (Thomas Eng)				
Betapress	16	5/8	600–1500	11/16
	23	7/16	860–2160	11/16
Express	20	1	800-2000	13/16
	25	5/8	1000 2500	11/16
	30	7/16	1200–3000	11/16
Unipress	20	1	970 2420	13/16
	27	5/8	1300–3270	11/16
	34	7/16	1640–4120	11/16
Novapress	37	1	760 3700	13/16
	45	5/8	900–4500	11/16
	61	7/16	1220–6100	11/16
BB3B	35	5/8	1490–2980	11/16
BB4	27	5/8	900–2700	11/16
	35	5/8	1167–3500	11/16
	45	7/16	1500 4500	11/16
Rotapress				
MarkIIA	37	1	710 3550	13/16
	45	5/8	1640–8200	11/16
	61	7/16	2220 11,100	11/16
Mark IV	45	1	2090–6000	15/16
	55	5/8	2550–7330	11/16
	75	7/16	3500 10,000	11/16
Fette equipment (Raymond Auto)				
		(mm)		(mm)
PT2080	29	25	435 2900	18
	36	16	540 4100	18
	43	16	645 4900	18
Perfecta 3000	37	25	4400	22
	45	16	6750	18
	55	13	10,500	18

begins and make suitable adjustments, if necessary. Check these properties routinely and regularly at 15–30 min intervals while the machine is in operation. When the batch has been run, turn off the power. Remove the hopper and feed frame from the machine. Remove loose granulation and dust with a vacuum line. Remove all pressure from the wheel. Remove the punches and dies in the reverse order of that used in setting up the machine. First, remove the upper punches individually, 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 gradually evolved into models capable of compressing tablets at high production rates. See Figs 90-19, 90-21, and 90-22. 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 90-23, 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 III, 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 90-24. Presses with triple compression points (see Table III) 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

Fig 90-21. Rotapress Mark IIA; designed for improvements in sound reduction, operator safety, cleanliness, and operational convenience; note control panel on front of machine (courtesy, Thomas/Manesty).

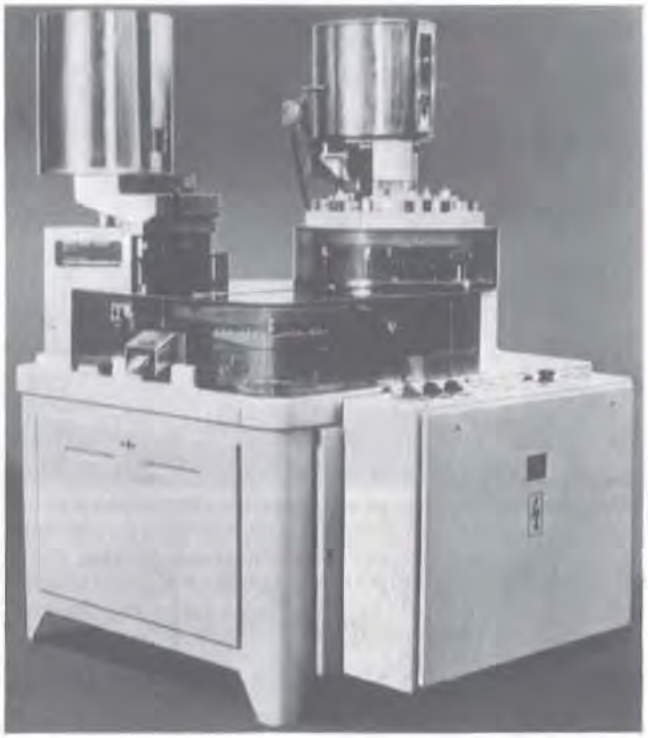


Fig 90-22. Mark II-A Rotapress with 61 stations to give an output of 11,000 tablets per minute and equipped with remote press control; the Thomas Sentinel II is shown on the left (courtesy, Thomas/Manesty).

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*). Press-coated tablets can be used to separate incompatible drug substances and also to give an enteric coating to the core tablets.

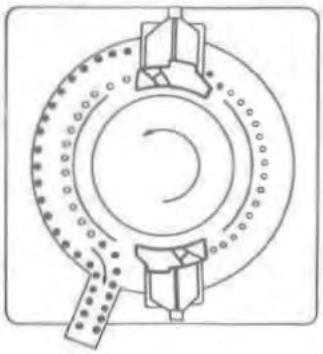


Fig 90-23. The movement of tablets on die table of a double rotary press (courtesy, Vector/Colton).

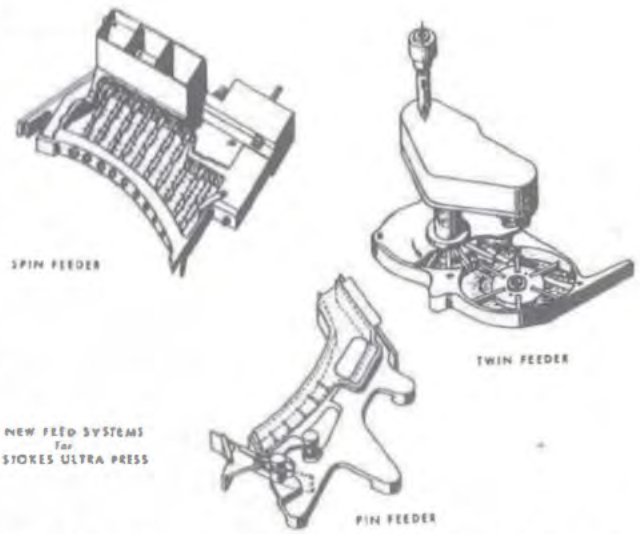
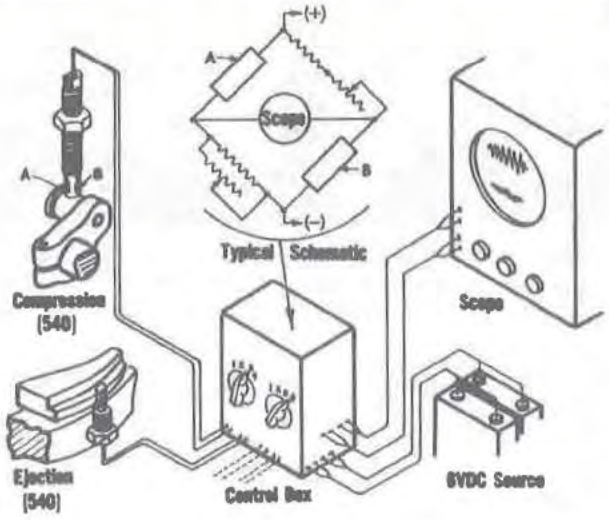


Fig 90-24. Feeding devices designed to promote flow of granulations for high-speed machines (courtesy, Stokes/Pennwalt).



Typical Layout - Rotary

Fig 90-25. Upper photo: High-speed rotary press equipped with strain gauges; Lower photo: layout showing arrangement of electronic components (courtesy, Upjohn).

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:

1. Excess "fines" or powder which traps air in the tablet mixture.
2. 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.
3. Worn and imperfect punches. Punches should be smooth and buffed. Nicked punches will often cause capping. The development of fine feather edges on tablets indicates wear on punches.
4. 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.
5. Too much pressure. By reducing the pressure on the machines the condition may be corrected.
6. Unsuitable formula. It may be necessary to change the formula.
7. Moist and soft granulation. This type of granulation will not flow freely into the dies, thus giving uneven weights and soft or capped tablets.
8. 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.

Fig 90-26. Fette Perfecta 3000 high-speed tablet press with pressing compartment completely sealed off from outside environment making cross contamination impossible (courtesy, Raymond Auto).

Instrumented Tablet Presses

Compressional and ejectional forces involved in tablet compression can be studied by attaching strain gauges to the punches and other press components involved in compression. The electrical output of the gauges has been monitored by telemetry or use of a dual beam oscilloscope equipped with camera.[16,17] Instrumentation permits a study of the compaction characteristics of granulations, their flowabilities, and the effect of formulation additives, such as lubricants. 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. Therefore definition of the compressional force giving a satisfactory tablet for a formulation provides an in-process control for obtaining both tablet-to-tablet and lot-to-lot uniformity (see Fig 90-25).

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. When tablet weights vary from preset limits, the monitor will automatically 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 Fig 90-22). 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.[18,19]

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, who received these products. This resulted in the industry spending thousands 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 utilizing 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 90-26, the pressing compartment is completely sealed off from the outside environment, making cross-contamination 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 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* sp, *E coli*, certain *Pseudomonas* sp 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 Food and Drug Administration (see page 1489)

Tablet Formulations

Wet Granulation Method

CT Acetaminophen, 300 mg

Ingredients	In each	In 10,000
Acetaminophen	3000 mg	3000 g
Polyvinylpyrrolidone	22.5 mg	225 g
Lactose	61.75 mg	617.5 g
Alcohol 3A—200 proof	4.5 mL	45 L
Stearic acid	9 mg	90 g
Talc	13.5 mg	135 g
Corn starch	43.25mg	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 granulation at 50°C overnight. Screen the dried granulation through a 20-mesh screen. Bolt the stearic acid, talc, and corn starch through 60-mesh screen prior to mixing by tumbling with the granulation. Compress using $^{7}/_{16}$-in 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	6.5mg	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 above first three ingredients with ethylcellulose (5%) dissolved in anhydrous ethyl alcohol adding additional anhydrous alcohol to obtain good wet granules. Wet screen through 8 stainless steel screen and dry at room temperature in an air-conditioned area. Dry screen through 20 stainless steel screen and incorporate the remaining three ingredients. Mix thoroughly and compress. Use a flat beveled, ¼-in punch. 20 tablets should weigh 2.39 g.

Chewable Antacid Tablets

Ingredients	In each	In 10,000
Magnesium trisilicate	500mg	5000 g
Aluminum hydroxide, dried gel	250mg	2500 g
Mannitol	300mg	3000 g
Sodium saccharin	2mg	20 g
Starch paste, 5%	qs	qs
Oil of peppermint	1 mg	10 g
Magnesium stearate	10 mg	100 g
Corn starch	10mg	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 $^{5}/_{8}$-in flat-face bevel-edge punch (courtesy, Atlas).

CT Hexavitamin

Ingredients	In each	In 7000
Ascorbic Acid USP (powder)[a]	82.5mg	577.5 g
Thiamine Mononitrate USP (powder)[a]	2.4 mg	16.8 g
Riboflavin[a]	3.3mg	23.1 g
Nicotinamide USP (powder)[a]	22 mg	154 g
Starch	...	97.4 g
Lactose	...	41.2 g
Zein	...	45 g
Vitamin A acetate:	6250 U	
Vitamin D_2[a] (use Pfizer crystalets medium granules containing 500,000 U vitamin A acetate and 50,000 U vitamin D_2/g).	625 U	87.5 g
Magnesium stearate		7.5 g
Weight of granulation		1050 g

[a] Includes following 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 8 stainless steel screen and dry at 110-120°F. Dry screen through 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 phenobarbital. Dry and put through a 12-mesh screen, add the remainder of the material, mix thoroughly, and compress into tablets, using a 13/32 in concave punch. 10 tablets should weigh 4.13 g.

Dry Granulation Method

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 14–16 mesh size. Recompress into tablets, using a 13/32 in punch. 10 tablets should weigh 3.575 g.

CT Sodium Phenobarbital

Ingredients	In each	In 7000
Phenobarbital sodium	65 mg	455 g
Milk sugar (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 14–16-mesh granules. Recompress into tablets, using a 9/32-in 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
Milk sugar (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 14–16 mesh granules. Recompress into tablets, using a 1/4-in 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 Method

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 twin-shell blender for 15 minutes and compress on 13/32-in 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 gm	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-in 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] Rehei's F-MA-11.
[b] Avicel.

Blend all ingredients in a suitable blender. Compress using 5/8-in 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 $^{3}/_{8}$-in 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 12–14 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 $^{11}/_{32}$-in 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 $^{7}/_{16}$-in 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 microcrystalline cellulose. Add spray-dried lactose and blend. Finally add the stearic acid and colloidal silica; blend to obtain homogeneous mixture. Compress using $^{9}/_{32}$-in 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, and 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 50–500 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 90-27). In some hand molds, as shown in Fig 90-28, the pegs are forced down onto the plate holding the moist trituration.

Fig 90-27. Hand molding tablet triturates (courtesy, MSD).

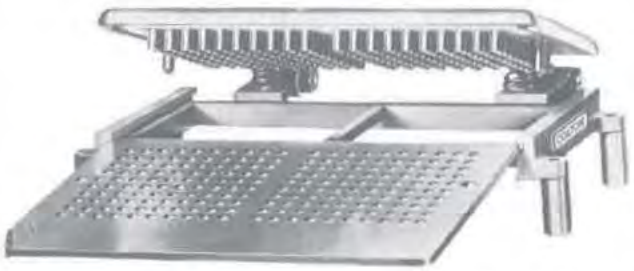


Fig 90-28. Tablet triturate mold (courtesy, Vector/Colton).

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 hy 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 now 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 completely filled, 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 immediately moistened and also forced into the perforations in the plate until they are completely filled. 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 thoroughly dried 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 89.

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; and 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 only be determined initially by experiment.

Hand-Molding Tablet Triturates

In preparing hand-molded tablets place the mold plate on a glass plate. The properly moistened material is pressed into the perforations of the mold with a broad spatula exerting uniform pressure over each opening. The excess material is removed by passing the spatula at an oblique angle with strong hand pressure over the mold to give a clean, flat surface. The material thus removed should he 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 90 29 makes tablet triturates at a rate of 2500/min. For machine-molding, the powder mass need not be as moist as for plate-molding since the time interval between forming the tablets and pressing them is considerably shorter. The moistened mass passes through the funnel of the hopper to the feed plates below. In this feed plate are four holes having the same diameter as the mouth of the funnel. The

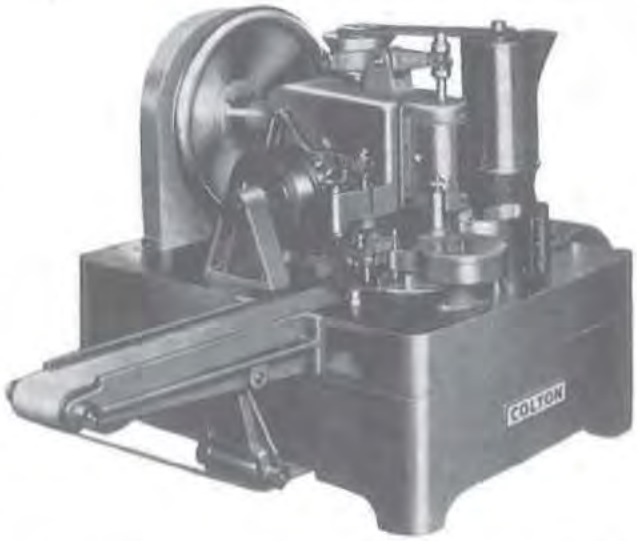


Fig 90-29. Automatic tablet triturate machine (courtesy, Vector/Colton).

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

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 is generally 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.

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.[20]

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 has already 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.[21]

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 classical capsule shape is illustrated in Fig 90-30. These capsules are filled by introducing the powdered material into the longer end or body of the capsule and then slipping on the cap. Hard gelatin capsules are made largely from gelatin, FD&C colorants, and sometimes an opacifying agent such as titanium dioxide; the USP permits the gelatin for this purpose to contain 0.15% sulfur dioxide to prevent decomposition during manufacture. Hard gelatin capsules contain 12–16% water, but the water content can vary depending on the storage conditions. When the humidity is low, the capsules become brittle; if stored at high humidities, the capsules become flaccid and lose their shape. Storage in high temperature areas can also affect the quality of hard gelatin capsules. Gelatin capsules do not protect hygroscopic materials from atmospheric water vapor as moisture can diffuse through the gelatin wall.

Companies having equipment for preparing empty hard gelatin capsules include Lilly, Parke-Davis, Scherer Gelatin Corp, and SK&F. The latter's production is mainly for its own use; the others are suppliers to the industry. With this equipment stainless steel pins, set in plates, are dipped into the gelatin solution, which must be maintained at a uniform temperature and an exact degree of fluidity. If the gelatin solution varies in viscosity, it will correspondingly 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 90-31 and 90-32. These show the stainless steel pins being

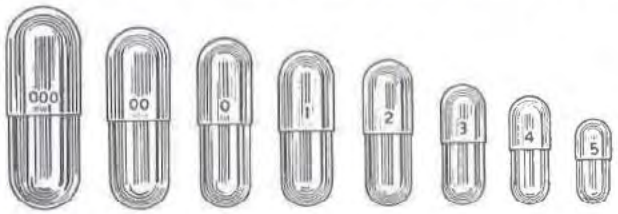


Fig 90-30. Hard gelatin capsules showing relative sizes (courtesy, Parke-Davis).

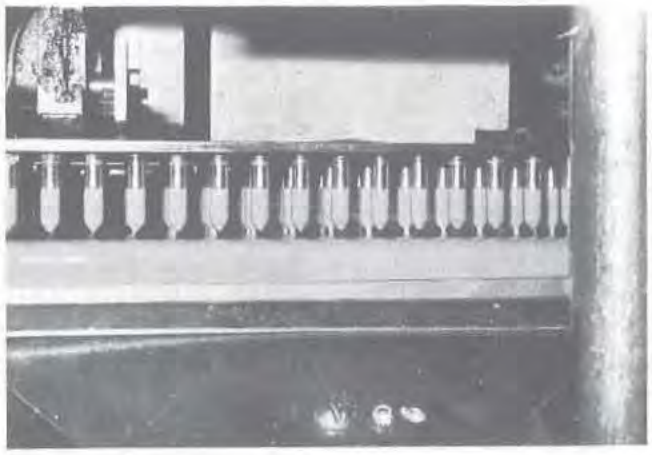


Fig 90-31. Manufacturer of hard gelatin capsules by dipping stainless steel pins into gelatin solutions (courtesy, Lilly).

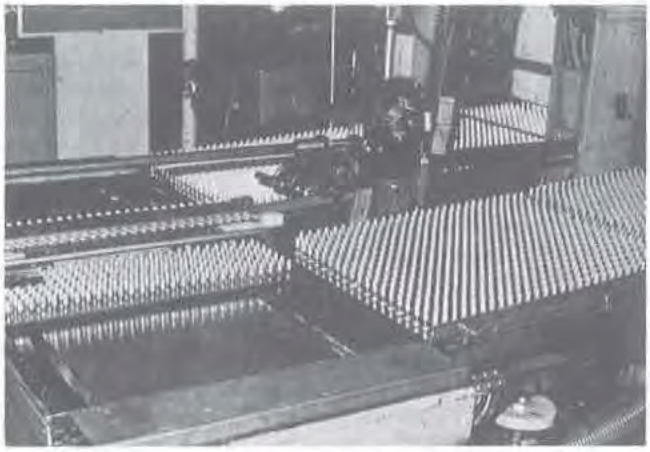


Fig 90-32. Formed capsules being dried by rotating through drying kiln (courtesy, Lilly).

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 90-30) 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 SK&F, which are of distinctive shape. For Lilly products, capsules are used in which the end of the base is tapered to give the capsule a bulletlike shape; products encapsulated in this form are called *Pulvules*. The SK&F 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 trade mark 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 the locking rings are engaged after filling, their length is equivalent to that of the conventional capsule.

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, will often 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 either 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 the 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 69. Granular powders do not pack readily in capsules and crystalline materials, especially those which consist of a mass of filamentlike crystals as the quinine salts, are not easily fitted 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 are usually 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. Fig 90-33 illustrates a capsule filling machine which was formerly known as the Sharp and 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/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 90-34 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 and Dohme machine.

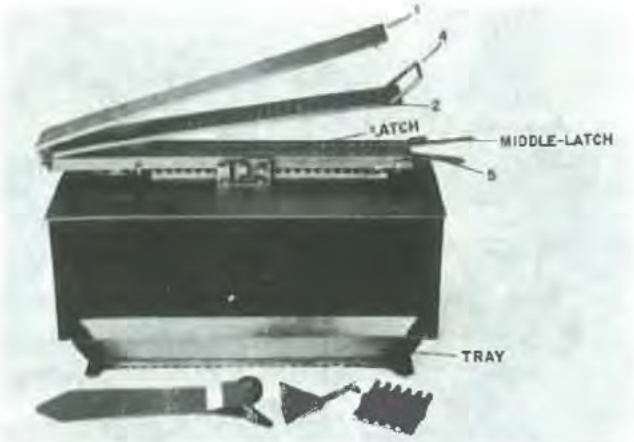


Fig 90-33. Hand-operated capsule machine (courtesy, ChemiPharm).

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, 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 are also frequently used. Because of the absence of numerous additives and manufacturing processing, the capsule form is frequently used 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.[22] 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.

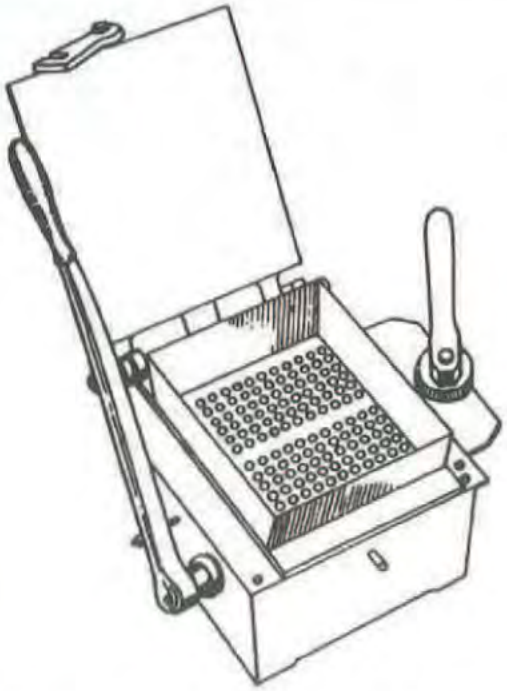


Fig 90-34. Hand-operated capsule machine, Model 300 (courtesy, ChemiPharm).

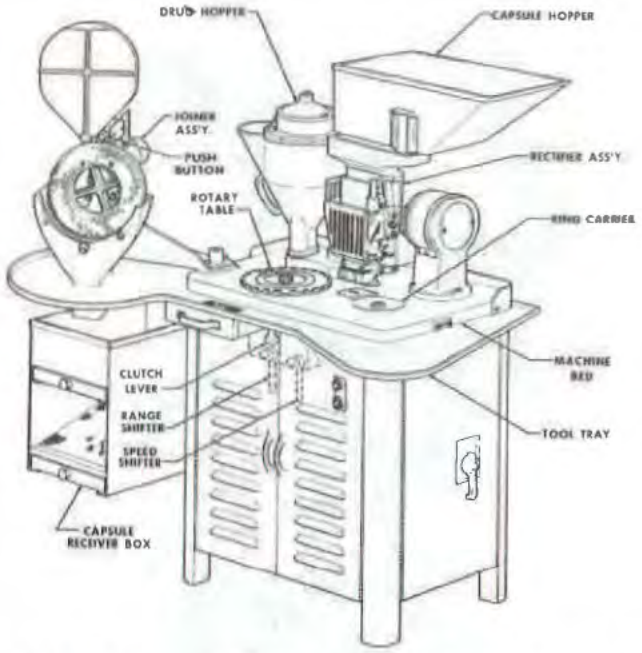


Fig 90-35. Schematic of Type 8 capsule-filling machine (courtesy, Parke-Davis).

Semiautomatic capsule filling machines manufactured by Parke-Davis and by Lilly are illustrated in Figs 90-35 and 90-36. The Type 8 capsule-filling machine performs mechanically under the same principle as the hand filling of capsules. This includes (1) separation of the cap from the body; (2) filling the body half; and (3) 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 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 are now located in the bottom ring, ready for filling.

The ring holding the body halves is rotated at one of 8 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

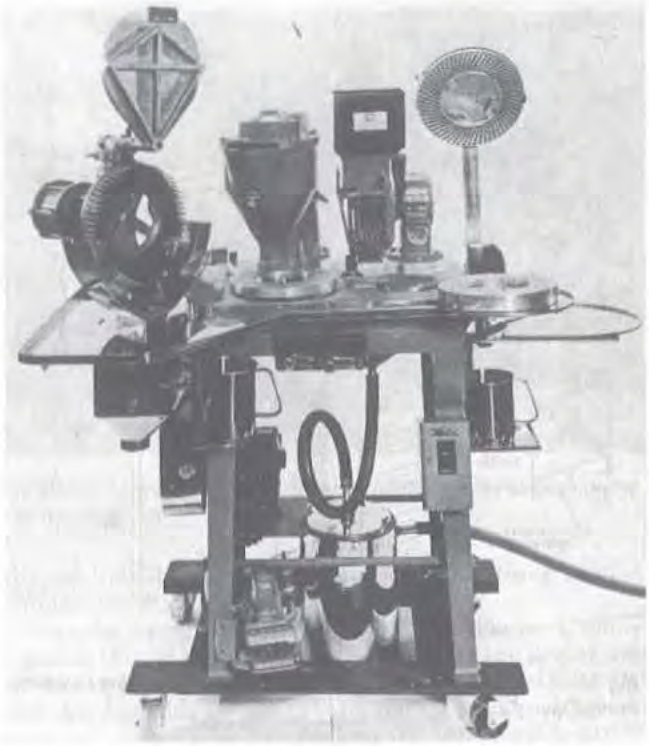


Fig 90-36. Type 8 capsule-filling machine (courtesy, Lilly).

in the ring. The peg ring pins are entered in the holes of the body holding ring and tapped in place by the air cylinder pushing the body halves back into the cap halves.

The holding ring assembly is now pushed by hand back onto the peg ring away from the joiner plate, thus pushing the capsules out of the holding ring assembly. The joined capsules then fall through the joiner chute into the capsule receiver box. The capsule receiver box screens the excess powder from the capsules and delivers them to any convenient container.

Many companies use the Type 8 capsule-filling equipment because of its ease of operation, low cost, and extreme flexibility. A Type 8 capsule filling machine will produce approximately 200,000 capsules/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.

Fig 90-37. MG-2, automatic capsule-filling machine (courtesy, Supermatic).

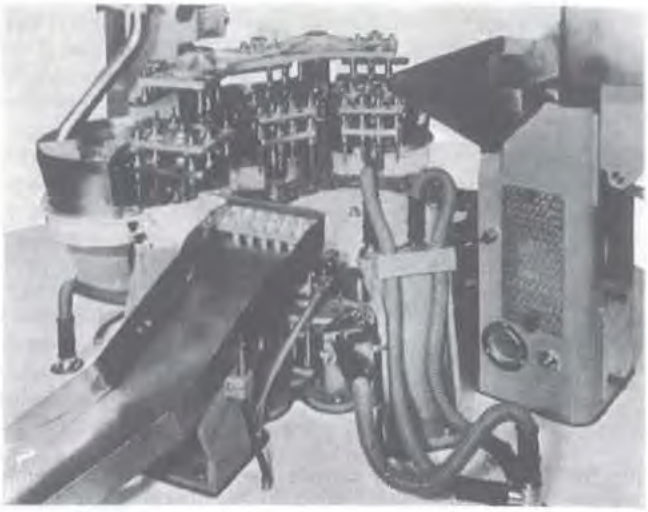


Fig 90-38. Zanasi automatic filling machine, Model AZ-60. The set of filling heads shown at the left collects the powder from the hopper, compresses it into a soft slug, and inserts it into the bottom half of the capsule (courtesy, United Machinery).

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 can also 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 then 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/hour can be obtained (see Figs 90-37, 38 and 39).

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 are then 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

Fig 90-39. Hoefliger & Karg automatic capsule filling machine, Model GFK 1200 (courtesy, Amaco).

50% or more, by weight, of the dosage form. See the official compendia for details of the procedures.

Disintegration tests are usually not required for capsules unless they have been treated to resist solution in gastric fluid (enteric-coated). In this case they must meet the requirements for disintegration of enteric-coated tablets. For certain capsule dosage forms a dissolution requirement is part of the monograph. Procedures used are similar to those employed in the case of compressed tablets. (See Chap 35).

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 are generally 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 are generally made so that the heat seam of the gelatin shell opens to release its liquid medication into the stomach less than five 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 the Upjohn Co. The sheets of gelatin may have the same color or different colors.

Fig 90-40. Rotary die elastic capsule filler.

Rotary Die Process

In 1933 the rotary die process for elastic capsules was perfected by Robert P Scherer.[23] 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 90-40. See also Fig 90-41.

Fig 90-41. Scherer soft elastic capsule machine (courtesy, Scherer).

By this process the content of each capsule is measured individually by a single stroke of a pump so accurately constructed that plunger travel of 0.025 in will deliver 1 ♏ (apoth). The Scherer machine contains banks of pumps so arranged that many capsules may be formed and filled simultaneously. All pumps are engineered to extremely small mechanical tolerances and to an extremely high degree of precision and similarity. All operations are controlled on a weight basis by actual periodic checks with a group of analytical balances. Individual net-fill weights of capsules resulting from large-scale production vary no more than ±1 to 3% from theory depending upon the materials used.

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

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 utilizes the Accogel machine and process which were developed in the Lederle Laboratories Div of the American Cyanamid Co. The Accogel, or Stern machine, uses a system of rotary dies but is unique in that it is the only machine that can successfully 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. The machine 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 could also 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.[24] 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.

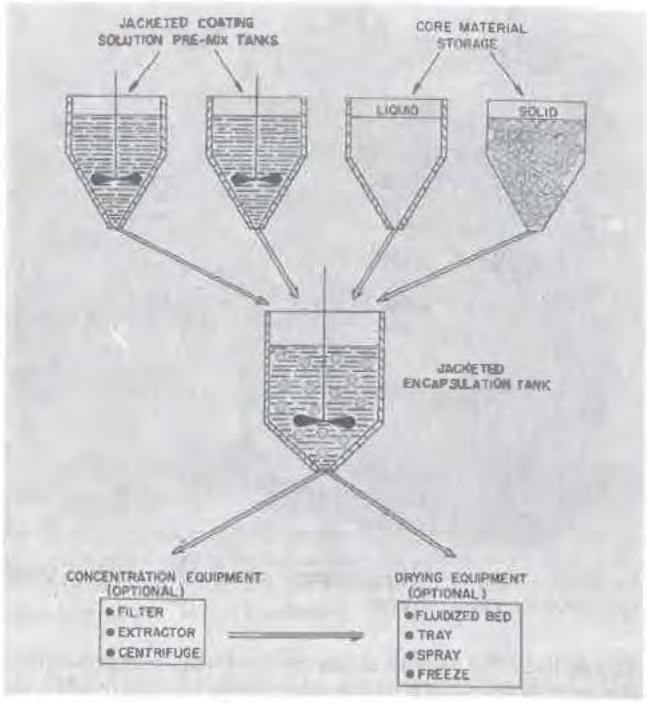


Fig 90-42. Production installation for microencapsulation process (courtesy, NCR).

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 utilizing 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; and (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. Fig 90-42 shows a typical flow diagram of a production installation.

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.

Other Oral Solid Dosage Forms

Pills

Pills are small, round solid dosage forms containing a medicinal agent and are intended for oral administration. Pills were formerly the most extensively used oral dosage form, but they have been largely replaced 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 readily broken, 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 gradually worked 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 boles are to be placed in troches or candy pieces, core rod tooling is used (see Fig 90-43). 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.

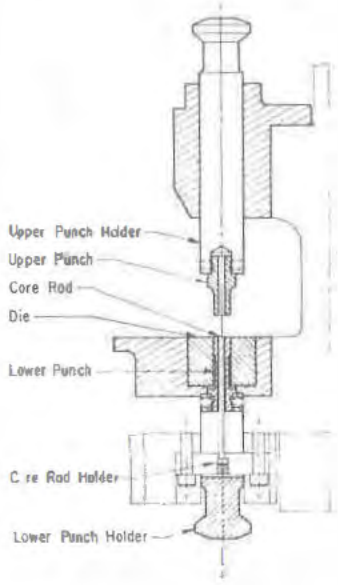


Fig 90-43. Core rod tooling for compressing troches or candy pieces with hole in center (courtesy, Vector/Colton).

Cachets

Related to capsules, inasmuch as they provide an edible container for the oral administration of solid drugs, cachets were formerly used in pharmacy. They varied in size from $\frac{3}{4}$ to $\frac{1}{8}$ 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 tightly sealed by moistening the margins and pressing firmly together. When moistened with water, their character was entirely changed; they became soft, elastic, and slippery. Hence, they could easily be swallowed by floating them on 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.[25] 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 91

Coating of Pharmaceutical Dosage Forms

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Introduction

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 is already functionally complete. In attempting to answer this question, if one examines the market, it will be immediately obvious that a significant proportion of pharmaceutical solid dosage forms are coated. The reasons for this range from the aesthetic to a desire to control the bioavailability of the drug, and include the following:

1. Protection of 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. Improvement in 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. Improvement in product mechanical integrity, since coated products are generally more resistant to mishandling (abrasion, attrition, etc).
9. Modification of 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, and although a great deal has been written about the materials and methods used, as a process it is still often recognized to be more of an art than a science, a factor which is obviously 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] describe 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).

A point that must be stressed is that much of the earlier coated products were produced by individuals working in pharmacies, particularly when extemporaneous compounding was the order of the day, and although responsibility for tablet coating has now been assumed by the pharmaceutical industry, skilled individuals still practiced their art until quite recently.

The earliest attempts to apply coatings to pills obviously resulted in variable products, and required the handling of single pills. These 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 completely coated. 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 failed to yield a uniformly coated product.[5] Initially, the first sugar coated pills seen in the US were imported from France *circa* 1842[5]; while Warner, a Philadelphia pharmacist, became among the first indigenous manufacturers in 1856.[6]

Methods for the coating of a large number of tablets are essentially derived from those used in the candy industry, where techniques were highly evolved, even in the Middle Ages. Today, most coating pans are fabricated from stainless steel, although early pans were made from copper owing to the fact that 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 to extract the moisture and dust laden air from the vicinity of the pan.

Further evolution in the coating process tended to remain somewhat static until the late 1940's and early 1950's, with the conventional pan being the mainstay of all coating operations up to that time. However, in the last twenty or thirty years there have been some significant advances made in coating technology, advances often pre-empted by 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 utilizing 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, has always been associated with the solvent system, which often used 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 tends to be maximized. Thus, film coating began as a process utilizing inefficient drying equipment, relying on highly volatile coating formulations for success and has

evolved into one in which the processing equipment is a major factor. The latter has been largely responsible for the return to an aqueous process.

Obviously, the advances in equipment design have also benefited the sugar coating process, where, because of Good Manufacturing Procedures (GMP) and the need to maintain product uniformity and performance, the trend has been toward fully automated processes. Nonetheless film coating tends to maintain a somewhat dominant position in the area of tablet coating.

Pharmaceutical Coating Processes

Basically, there are four major techniques for applying coatings to pharmaceutical solid dosage forms: (1) Sugar Coating, (2) Film Coating, (3) Microencapsulation and (4) Compression Coating.

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

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

Microencapsulation is a modified form of film coating, differing from the latter only in the size of the particles (or liquid droplets) to be coated and the methods by which this is accomplished. It is based on either mechanical methods such as pan coating, air suspension techniques, multi-orifice 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 tabletting 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, the fact that it involves a mechanically complex operation has obviously been a prime factor in limiting its adoption as a popular technique.

The latter two approaches fall outside the scope of this chapter, which will be confined to processes in which liquid systems are applied to the surface of a solid dosage form, no matter how diverse that substrate might be. See Chapter 90.

Sugar Coating of Compressed Tablets

Sugar coating, as the name implies, is a process which relies on the use of two main raw materials, namely sucrose and water. Sugar is a somewhat generic term that lends itself to a whole class of materials. For the purposes of sugar coating, the only material which has stood the test of time is sucrose. The main reason for this, is that based on the techniques evolved, it is probably the only material which has enabled smooth, high quality coatings to be produced, which are essentially dry and tack free at the end of the process.

Although other methods for the coating of solid dosage forms have been and are being evolved, a significant proportion of all coated products are still sugar-coated, and some companies are spending vast amounts of capital to thoroughly update 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 multi-step process, where success is still measured in terms of the elegance of the final product, it has been, and still is in many companies, highly dependent on the use of skilled manpower. These factors, combined with a certain amount of folklore, are responsible for the process being long and tedious. However, processing times have gradually been improved 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 the following stages: (1) Sealing, (2) Subcoating, (3) Smoothing, (4) Coloring, (5) Polishing, and (6) Printing.

Sealing The sealing coat is applied directly to the tablet core for the prime purpose of separating the tablet core (and active ingredients contained therein) from the aqueous solutions used in the remainder of the coating process. 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 its use can lead to problems of impaired bioavailability owing 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 obviously depend on the tablet size and pan charge. However, another important factor is the tablet porosity, since highly porous tablets will tend to soak up the first application of solution, thus preventing it from spreading uniformly throughout the whole tablet mass. Thus, one or more further applications of resin solution may be necessary to ensure the cores are sealed.

Since most sealing coats develop a degree of tack at some time during the drying stages, their use is usually accompanied by one or more applications of 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 this material 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 build-up, 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.

If an enteric coated product is desired, it is usually achieved at the seal coat stage by extending the number of applications made, preferably using an enteric coating polymer 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 leads to a 50–100% weight increase, and it is at the subcoating stage that most of the build-up occurs, mainly to develop the basis of an elegant tablet profile.

Historically, subcoating has been achieved by the application of a gum-based solution to the sealed tablet cores, and once this has been uniformly distributed throughout the tablet mass, to follow 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 build-up has been achieved. Thus, in this situation, the subcoating is a sandwich of alter-

Table I—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 II—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	—

Table III—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

nate layers of gum and powder. Some examples of binder solutions are shown in Table I, and those of dusting powder formulations in Table II.

This approach has proved to be very effective, particularly where there is difficulty in covering edges, etc. However, 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 very weak, but also, dust will collect in the back of the pan, a factor which may contribute to ultimate 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, in which the powdered materials responsible for coating build-up have been incorporated into a gum-based solution. An example of such a formulation is shown in Table III. Obviously, 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 produce satisfactory subcoats with the minimum of problems.

Smoothing—Depending on how successfully the subcoat was applied, there may be a necessity for further smoothing to be achieved prior to color coating, particularly if the latter is to be accomplished by means of a dye coating process. Smoothing can usually be accomplished by the application of a simple syrup solution (approximately 60 70% sugar solids).

Often the smoothing syrups contain a low percentage of titanium dioxide (1–5%) as an opacifier. This can be particularly useful when following with a dye color coating process since it makes the layer under the color coating more reflective, resulting in a brighter, cleaner ultimate color.

Color Coating—In many ways, color coating is the most important step in the successful completion of a sugar coating process. This is achieved by the multi-step application of simple syrup solutions (60–70% sugar solids) containing the requisite coloring matter. The types of coloring materials used can be divided into two categories: dyes and pigments. The distinction between the two is simply 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 utilized by a skilled artisan, water-soluble dyes produce the most elegant of sugar coated tablets, mainly because they yield a much cleaner, brighter color. However, since water-soluble dyes are migratory colorants (that is to say, as the moisture is drawn out of the tablets, this will tend to cause migration of the color, leading to a nonuniform distribution of color), great care must be exercised in their use, particularly when dark shades are required. This involves the application of volumes of coating solution (containing low concentrations of colorant), which are capable of just wetting the entire tablet mass, and then allowing the tablets to dry very slowly to prevent color migration. 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.

Finally, in order to achieve the requisite color uniformity and intensity, it may be necessary to make 60 repeat applications of color solution. 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 completely opaque, or the system is formulated 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 application can be dried more rapidly, significant savings can be made in processing times.

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 with the former, it is necessary to ensure that all the insoluble matter is completely wetted and dispersed. Thus the use of prepared pigment color concentrates, which are commercially available, is usually beneficial.

Polishing—In order to impart the requisite gloss to the final product, the tablets, when dry, are submitted to a polishing process where wax mixtures (beeswax, carnauba wax, candelilla wax, hard paraffin wax, etc) are applied either as finely divided powder mixtures or as suspensions or solutions in various solvents to the tablets in wax or canvas-lined pans.

Printing—In order to identify sugar-coated tablets apart from shape, size, and color, it is often necessary to submit them to a printing stage, either prior to or subsequent to the polishing stage, 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 constantly tumbling can present difficulties if the tablets are not strong enough to withstand the stress encountered. 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 solid particulate matter exceeds the capacity of the binder in the formulation, creating soft coatings or those with increased tendency to crack.

Color nonuniformity is a common problem, particularly when water-soluble dyes are used. Since the latter have a tendency to migrate easily, lack of control over the drying phases during the process can result in nonuniform distribution of the coloring material. Rough tablets are obtained either as the result of too rapid drying or lack of uniform distribution of coating fluid after each application. This is particularly troublesome during the color coating stage, when the problem may be highlighted as "marbling" after subsequent polishing.

Film Coating of Solid Dosage Forms

Film coating involves the deposition of a thin, but uniform, membrane 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 are essentially 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 1950's in order to combat the shortcomings of the then predominant sugar coating process. That it has proven successful must be attributed to its major advantages which include:

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

The major process advantages were derived from the greater volatility of the organic solvents used. However, in spite of its success, there has always been an awareness that certain disadvantages could prove ultimately to be a limiting factor.

These disadvantages are mainly attributed to the organic solvents used in the process and include:

(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, in the interim since its introduction, significant advances have been made in process technology and equipment design. The emphasis has changed from requiring the presence of highly volatile organic solvents so that the product dries rapidly, to achieving 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 aqueous systems.

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

A major requirement for the polymer is solubility in a wide range of solvent systems to promote flexibility in formulation. In addition, it must possess an ability to produce coatings which have suitable mechanical properties. Because of the various requirements of the coating, such as being exposed to gastrointestinal fluids, the polymer should meet certain performance characteristics.

Cellulose ethers constitute the majority of polymer types used for 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, which are copolymers of methacrylic acid and methyl methacrylate.

Most polymers are employed as solutions in either aqueous or organic solvent based systems. An alternative system utilizes certain water-insoluble polymers such as ethylcellulose and/or some of the acrylics as aqueous dispersions. An additional factor to be considered in the selection of polymers concerns the various molecular weight grades available for each type. 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 lends flexibility to the film, thus better able to withstand stress. This 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 a degree of permanence if the properties of the coating are to be stable on storage. Examples of typical plasticizers include glycerin, propylene glycol, polyethylene glycols, triacetin, acetylated monoglyceride, citrate esters (eg, triethyl citrate) and phthalate esters (eg, diethyl phthalate).

Colorants are usually used to enhance the aesthetic appeal of the product as well as to increase product identification. However, under certain circumstances, they can enhance certain necessary physical properties of the applied film coats. As in the case of sugar coating, colorants can either be classified as water-soluble dyes or insoluble pigments.

The use of water-soluble dyes is precluded with organic solvent based film coating because of lack of solubility in the solvent system. Thus, the use of pigments, particularly the aluminum lakes, provides the most useful means of coloring film coating systems. Obviously, in aqueous film coating there is potential for using water-soluble dyes as colorants, although in fact, pigments still offer some significant advantages for the following reasons:

(1) The tendency of some water-soluble dyes to interfere with bioavailability[11]
(2) The possibility of reduction in permeability of the coating to moisture when pigments are used[12]
(3) Pigments serve as a bulking agent to increase overall solids content in coating system.

The major solvents used in film coating typically belong to one of the following classes: alcohols, ketones, esters, chlorinated hydrocarbons, and water. Solvents serve to perform an important function in the film coating process, since they facilitate the delivery of the film forming materials to the surface of the substrate. Good interaction between solvent and polymer is necessary to ensure that optimal film properties are derived when the coating dries. This initial interaction between solvent and polymer will yield maximum polymer chain extension, producing films having the greatest co-

hesive strength, and thus, best mechanical properties. An important function of the solvent systems is also to assure a controlled deposition of the polymer onto the surface of the substrate if a coherent and adherent film coat is to be obtained.

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

Modified Release Film Coatings

Film coatings can be applied to pharmaceutical products in order to modify the release pattern of a drug. One form of coating is used to prevent the release of drugs in, or protect drugs from the effects of, the gastric environment. Such a coating is commonly called an *enteric* coating. Other types of coatings, often called *sustained* or *controlled release* coatings, are primarily used to extend the release of a drug over a long period of time.

Enteric Coatings By definition, enteric coatings are those which remain intact in the stomach, but will dissolve and release the contents of the dosage form once they arrive at the small intestine. Their purpose 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, they can be used to give a simple repeat-action effect where unprotected drug coated *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, many modern 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.

Historically, the earliest enteric coatings utilized formalin-treated gelatin, but this was unreliable since the polymerization of gelatin could not be accurately controlled, 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 was a potential to increase the degree of polymerization on storage, often resulting in failure to release the active contents. Although the pharmaceutical literature has contained references to many potentially suitable polymers, only three or four remain in use.

The most extensively used polymer is cellulose acetate phthalate (CAP) which is capable of functioning effectively as an enteric coating. However, a pH greater than 6 is required for solubility and thus a delay in drug release may ensue. It is also relatively permeable to moisture and gastric juice compared to most enteric polymers, thus susceptible to hydrolytic decomposition. Phthalic and acetic acids can be 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 juice, more stable to hydrolysis, and able to ionize at a lower pH, resulting in earlier release of actives in the duodenum.

A more recently available polymer is hydroxypropyl methylcellulose phthalate. This has similar stability to PVAP and dissociates in the same pH range. A final example of currently used polymers are those based on methacrylic acid—methacrylic acid ester copolymers with acidic ionizable groups. They have been reported to suffer from the disadvantage of having delayed breakdown even at relatively high pH.[13]

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 has also 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 rapidly released 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 slowly dissolved or decomposed in the gastrointestinal 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 particle 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.

Traditionally, the common method of producing a sustained release product has involved one of the following approaches.

A granulation containing the drug which could be *spheronized* prior to drying, if desired, is prepared. Dried granules are coated and then either filled into capsules or compressed into tablets. Alternatively, drugs are applied either in solution or as a suspension, to the surface of sugar *seeds* (nonpareils). These are subsequently coated with the requisite material and usually filled into capsules. In both cases, a fraction of uncoated granules or seeds may be included to provide an initial immediate release of drug.

In another approach, tablets may be coated with a suitable retardant film. A recent example of this approach includes the coating of a tablet core, containing an osmotically active material, in addition to the drug, with a semipermeable membrane. Subsequent to coating, an orifice of predetermined size is made in the coating by means of a laser beam. When such a tablet is swallowed, gastrointestinal fluids permeate the film, causing the contents of the dosage form to dissolve. The osmotic pressure created inside the membrane forces the drug to be diffused through the orifice at a controlled rate, usually following apparent zero order kinetics. This is, in effect, a very simple form of osmotic pump.

In spite of the various ingenious approaches employed in the creation of oral sustained release dosage forms, the limiting factor in all cases is based on gastrointestinal transit

times. One important consideration with any form of modified release coating, since the dose of drug used is often much higher than that used in conventional formulations, is to prevent "dose dumping." This can occur when the integrity of the coating is prematurely broken, either as a result of tablets sticking together during the coating process and becoming subsequently broken apart, or cracking of the coating anytime subsequent to processing.

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 may be readily 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.

Typical process-related problems that can occur during the coating process include *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, and *orange-peel* or *roughness*. The latter 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 color nonuniformity, 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 can also result from poor pigment dispersion in the coating solution

Finally, two significant problems which may occur result from the internal stress that develops within the film as it dries. The first occurs when this stress exceeds the tensile strength of the film, causing it to crack. The second is manifested as "bridging of a logo" (ie, a monogram present in the surface of the tablet core), and occurs when a component of the internal stress is able to overcome the localized forces of attachment of the film to the tablet in the region of the monogram. The film no longer follows the contour of the indented monogram and draws away to bridge the crevices, an unacceptable state.

A fundamental approach to formulation of the coating, in which the behavioral characteristics of materials, particularly the polymer used in the coating, is advocated[14] as providing a solution to such problems resulting from the effects of internal stress.

Coating Procedures and Equipment

Coating Pans—The coating of tablets by means of the sugar coating process has historically involved the manual application of the various coating fluids to a cascading bed of tablets in a conventional coating pan (Fig 91-1), 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 fully dispersed throughout the batch. To facilitate the uniform transfer of liquid, the tablets are often "stirred" by hand, or in larger pans, by means of a rake, to overcome mixing problems often associated with "dead spots," an inherent feature 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.

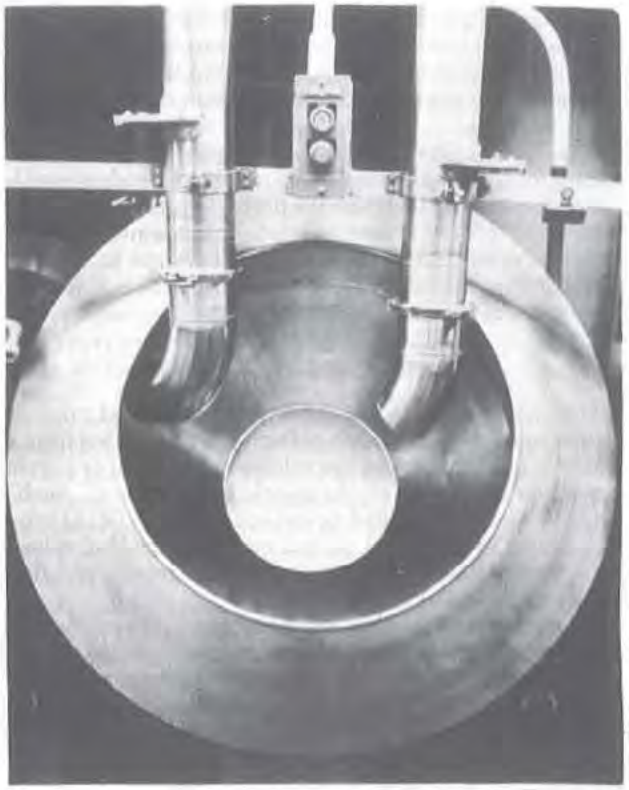


Fig 91-1. Typical equipment set-up for conventional sugar coating.

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

(1) Airless (or hydraulic) spray, where coating liquid is pumped under pressure to a spray nozzle, and atomization of the liquid occurs as it emerges from a very small aperture. 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.

The former is typically used in large-scale film coating operations for organic solvents, while the latter is more efficient in either a small-scale laboratory set-up, or in the currently popular aqueous film coating operations.

The use of spray techniques permits the delivery of finely atomized droplets of a coating solution, to the tablet mass in continual motion, in such a manner as to ensure uniform coverage while preventing adjacent tablets from adhering 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 91-2. The spray process can be operated either as an intermittent or continuous one.

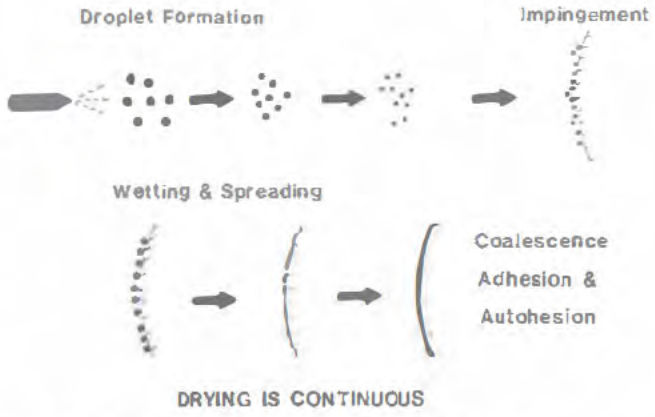


Fig 91-2. Schematic representation of the film coating process.

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 (and their inherently higher delivery rates), with organic solvent based formulations on a production scale, gave rise to an intermittent spray procedure. This allowed excess solvent to be removed during the nonspray part of the cycle, and thus reduced the risk of *picking* and tendency for tablets to stick together. However, in the ensuing 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, usually in a shorter time and simplifies the 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 poorly suited 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 this type of equipment. Considering the limitations in both air exchange and mixing capabilities, both must be significantly improved to assure that uniform and high drying rates are available to yield acceptable processing times with minimal risk to product integrity.

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 91-3), 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 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 over-all design ensure that the Pellegrini pan is more suitable for film coating, including aqueous-based coating solutions, than the conventional equipment previously discussed. Currently, Pellegrini pans are available with capacities ranging from the 10 kg laboratory

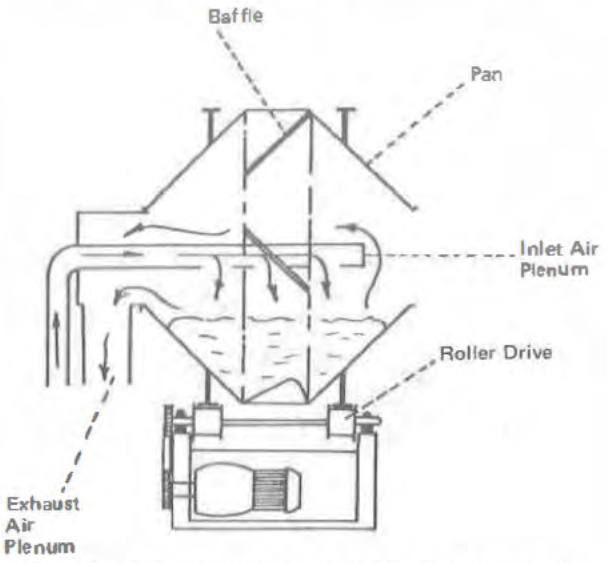


Fig 91-3. Schematic diagram of a Pellegrini coating pan.

scale-up to 1000 kg for high output production. A variant of the Pellegrini pan is the Hush Coater which has extra insulation to reduce the noise level in the pan.

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 submersed void onto the periphery of which coating solution is applied from a spray gun located in the opening of the supply air duct (Fig 91 4). Exhaust air is taken from the pan in a somewhat conventional manner.

A second approach, called the Immersion Sword Process, utilizes 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

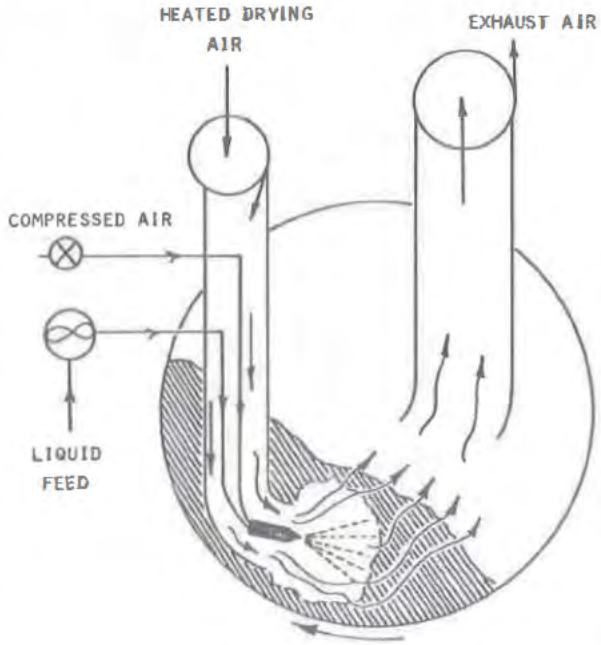
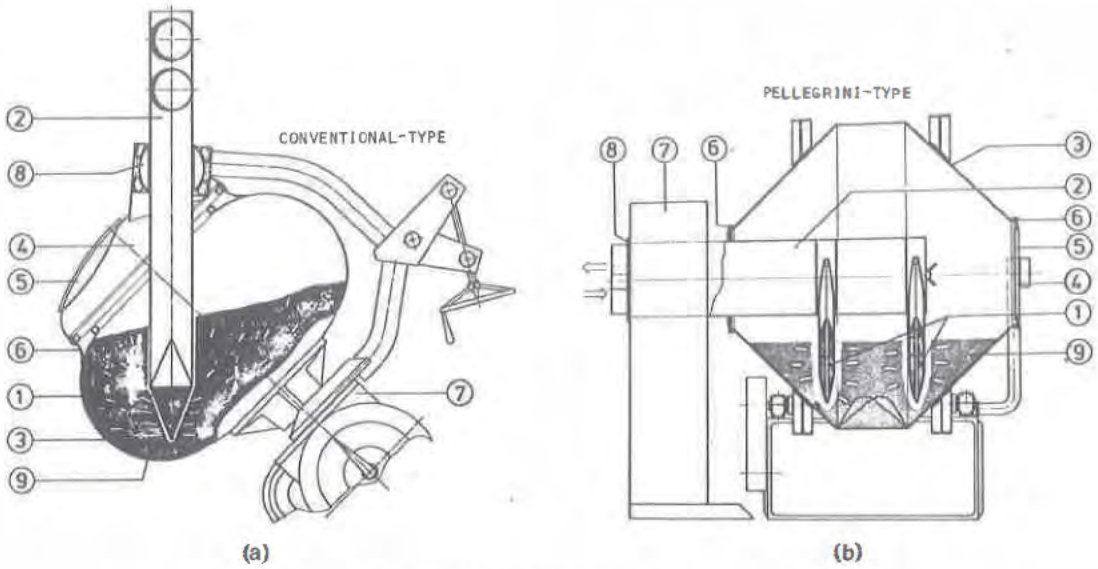


Fig 91-4. Schematic diagram of Strunck immersed tube coating apparatus.



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 91-5. Schematic diagram of the immersed sword apparatus for use in either (a) a conventional pan or (b) a Pellegrini pan.

exhaust air chamber for venting to the outside. This equipment is currently adaptable to both conventional and Pellegrini type pans (see Fig 91-5). Recently, the manufacturers of the Pellegrini pan have introduced a modification to the inlet air supply which permits drying air to be introduced underneath the tablet bed as well as being applied across the surface. A Pellegrini pan so modified is known as a Fast Dry Coater.

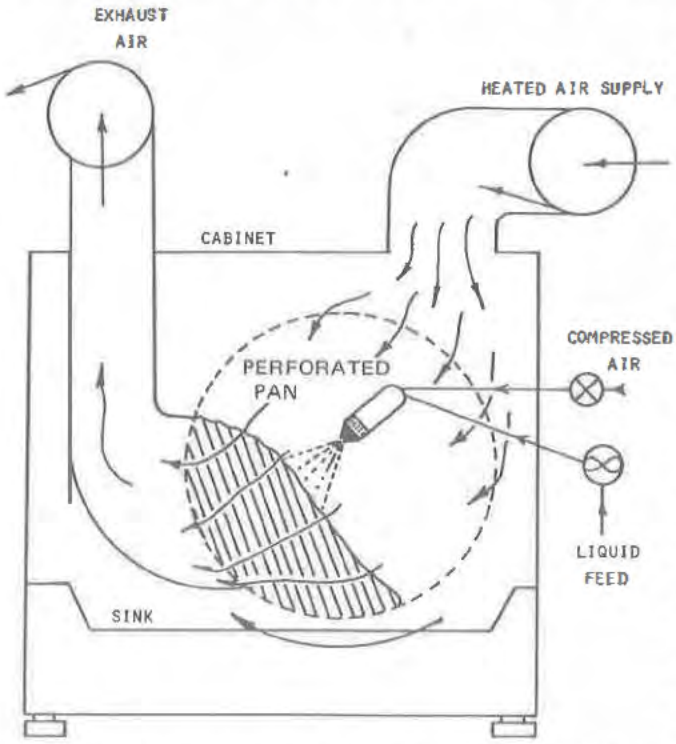


Fig 91-6. Schematic diagram of a 48-in Accela Cota (150 kg capacity).

A major contribution to film coating processing technology was made by the introduction of the Accela-Cota, an invention of the Eli Lilly Company. This is also an angular pan rotating on a horizontal axis. The major difference from the Pellegrini pan is that the flat portion of the pan periphery is completely perforated, enabling air of the required volume and temperature to be introduced into the cabinet surrounding the pan from above, and exhausted from a plenum in contact with the pan and positioned directly below the cascading bed of tablets (Fig 91-6). The presence of baffles in the pan augments the high efficiency in air exchange to ensure that processing times can be kept to a minimum. Capacities for this equipment range from the 10-15 kg laboratory scale-up to approximately 700 kg for the 66-in model. On the production scale, unloading is facilitated by the use of the Accela-scoop.

A variation on the concept of side vented pans is afforded by the Hi-Coater. In contrast to the Accela-Cota, the entire perforated area is replaced by four perforated panels linked to air ducts which make contact, at regular intervals during each pan revolution, with an exhaust plenum. Although not immediately obvious, this does permit continuous venting of air from the pan since at least one complete panel, or parts of two of the same, are always in contact with the plenum. Another contrast is evident from the fact that heated air is introduced directly into the front opening of the pan rather than into the cabinet surrounding it (Fig 91-7). Capacities for the Hi-Coater range from a 300 g (mini) to the 700 kg model HCF-200, with unloading in the production equipment being accomplished by means of a port in the pan periphery enabling discharge to be made directly into a bin placed beneath the machine.

Another alternative to pan equipment having rapid drying capabilities is the Driacoater (Fig 91-8), although this utilizes a totally different and somewhat novel approach. Unlike the two previous pieces of equipment, heated air is introduced into

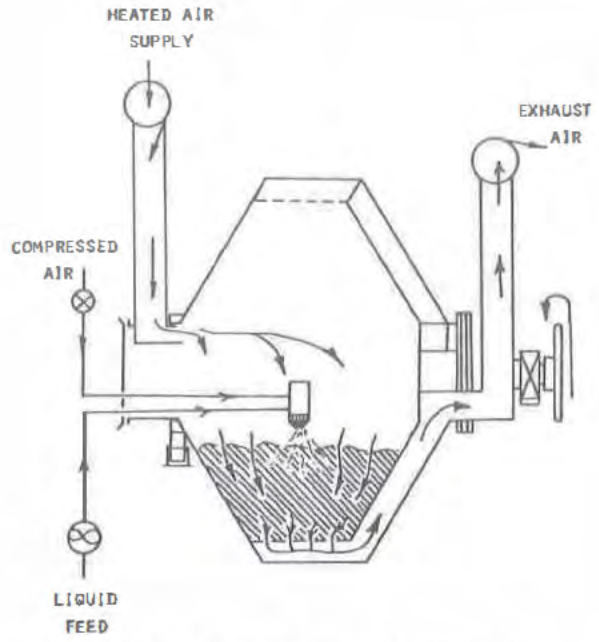


Fig 91-7. Schematic diagram of the HI-coater.

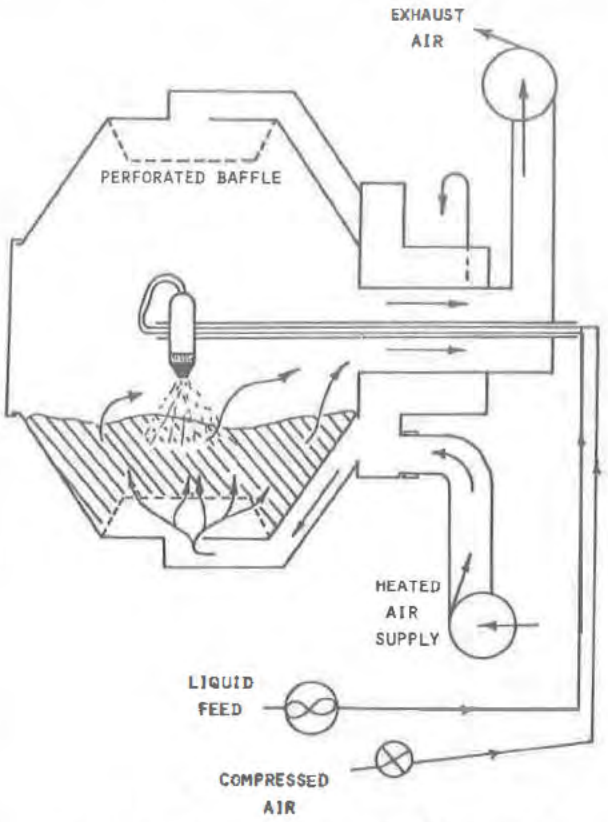


Fig 91-8. Schematic diagram of the Driacoater.

the back of the cascading bed of tablets by means of ducts, fixed to the outside of the pan, linked to perforated "baffles" fitted to the inside of the pan. This has the effect of partially lifting the tablets and acts as an aid to mixing. Air is then exhausted from the rear of the pan in a similar manner to that in the Pellegrini. Thus, drying is counter current to the spraying of coating solution. One claim for this equipment, which seems to have been substantiated, is that it tends to be less stressful on the tablets, causing less abrasion. The laboratory model of this equipment holds approximately 5 kg and production models, which are unloaded on reversing the pan via a chute attached to the front of the pan, can handle up to 1000 kg. The list of side-vented pans available was completed recently by the introduction of the Glatt-Coater, having capacities ranging from 25 to 1000 kg.

Because of a growing requirement for coating drug dosage materials smaller in size than conventional tablets (eg, granules and nonpareils), many of the manufacturers of perforated pans offer suitable equipment modifications for this purpose. Although the evolution that has taken place in coating pan design was done expressly to facilitate film coating, particularly when water is the solvent, the advances in processing technology that are derived are readily adaptable to the sugar coating process. Obviously the requirements for in-process drying need not be as rigorous as those for film coating.

Fluidized Bed Coating Equipment—Many exponents of this type of equipment will argue, often justifiably so, that it represents the ultimate in drying efficiency since the tablets are supported on a column of moving air allowing for a high area of contact between the drying medium and the species from which solvent must be removed rapidly. The nature of the fluid-bed process, however, essentially restricts its use to film coating. Tablets film coated by the fluidized bed method are often associated with a higher level of gloss, mainly because the coating solution impinges upon them before much solvent loss has occurred. One possible cause for criticism relates to the potential for more tablet damage to occur owing to the rigorous treatment received. High tablet hardness is not necessarily the major prerequisite here, but low tablet friability.

The earliest fluidized bed coating equipment was based on the Wurster design, (Fig 91-9). A moving bed of tablets

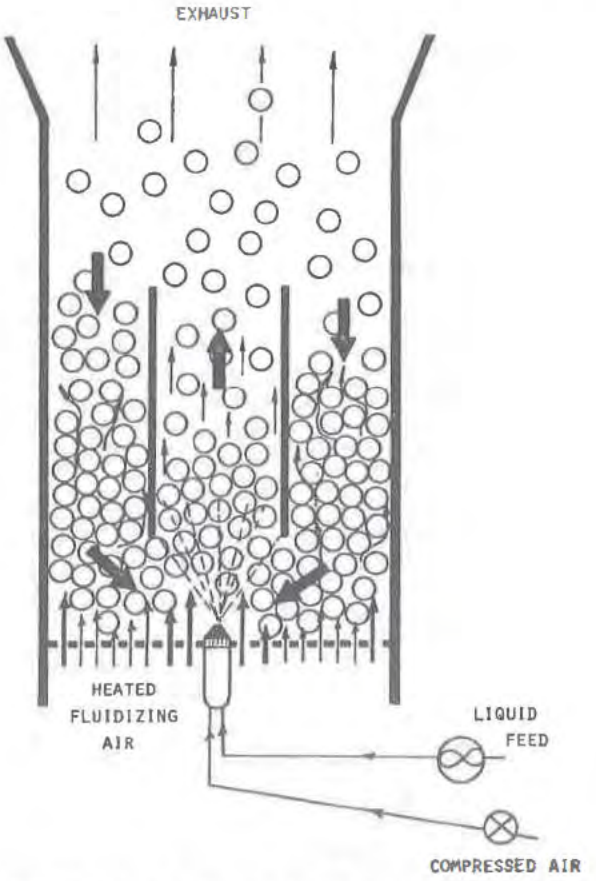


Fig 91-9. Schematic diagram of the Wurster fluidized bed coater. Perforations in air distribution plate are designed to control direction of particle movement.

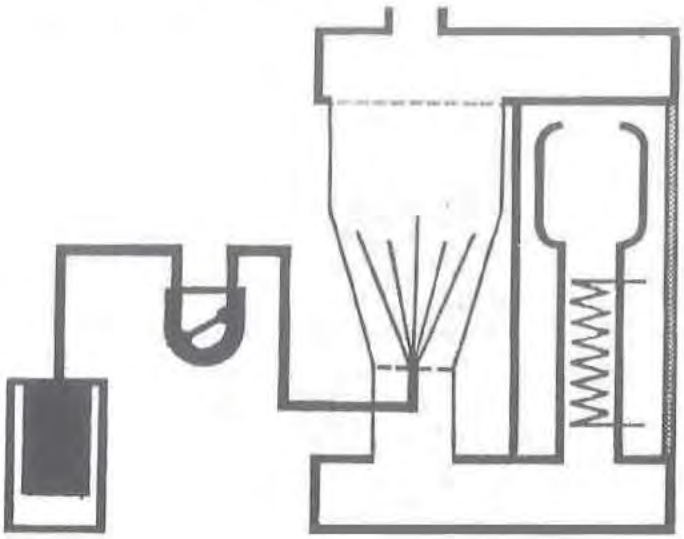


Fig 91-10. Schematic diagram of an Aeromatic fluidized bed coater.

continuously passes up the central column and, as a result of the effect of an expansion chamber at the top which reduces air velocity, the tablets drop back to the bottom between the walls of the inner and outer chamber. The concept of the equipment is based on a single spray gun situated in the center of an air distribution plate. The geometric proportions of the inner and outer columns are such that a continuously moving column of tablets passes through the spray path with every tablet capturing some of the coating and at the same time ensuring that little or no solution reaches the wall of the inner column.

While laboratory models are usually equipped with either 6 in or 12 in diameter outer chambers (having capacities in the range of 1–2 kg and 10-15 kg respectively), production models are usually based on an 18 in chamber diameter. Any attempt to increase the diameter while retaining only a single spray gun usually results in some tablets passing through the spray zone without receiving any coating. Consequently, large models utilize multiples of the 18 in concept; for example, the 32-in model has three inner coating partitions and spray guns, while the 46-in model has seven, all based on the 18-in model geometry, allowing for capacities up to approximately 400 kg.

An alternative in the fluid bed approach is afforded by the Aeromatic (Fig 91-10). Although this exhibits many similarities to the Wurster principle, it lacks the inner coating partitions. Laboratory units having a 0.5 to 2 kg capacity are available, together with production models handling up to 100-200 kg.

A third type of design is seen with the Flo-Coater. This also does not utilize the principle of an inner coating partition, and in addition prefers to locate the spray guns in the column wall and angled downwards (Fig 91-11). Current commercial equipment available is with capacities ranging from 1 to 500 kg.

Most, if not all, of the commercially available column coating equipment is also readily adaptable for the coating of powders, small particles, granules and seeds (non-pareils). In addition, they also tend to complement the fluidized bed drying and granulating equipment already manufactured by the various suppliers.

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. Increasing familiarity with, and understanding of, tablet

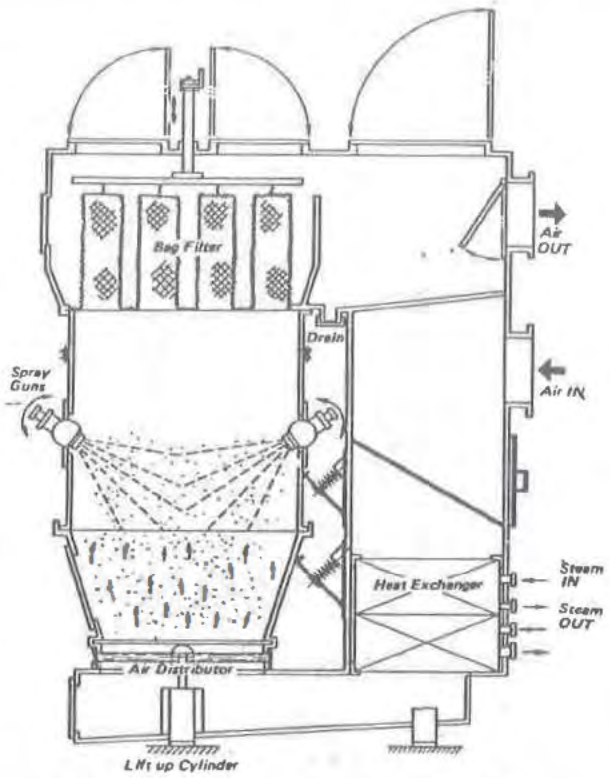


Fig 91-11. Schematic diagram of the Flo-coater.

coating as a unit process, and a desire to ensure compliance with GMP's, have increased ultimately the desire for assuring uniformity to design specifications every batch of product made. Obviously, this is difficult for any process where the idiosyncracies of individual operators must have a significant impact.

Total automation of the process can provide a solution to these problems. This involves developing a process where all the important variables and requisite constraints are predetermined. These can then 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 will be only as good as those peripheral devices used to detect various process conditions such as air flow, temperature and humidity, application volumes, and delivery rates, etc.

Since a sugar coating process has always 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 variety of coating fluids used in a single process. That it has been accomplished is evidenced by the number of commercially available systems that have been introduced.[18] The technology for automated control of sugar coating processes is now being adapted for film coating.

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 availiability. 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. 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 90).

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 are usually 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 through use of 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 adversely affected 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 may also be tested at conditions which are exaggerated from the normal. This is usually done for the purpose of accelerating changes so that an early extrapolation can be made 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).

Stability tests are usually 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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