Chapter 89

Tablets, Capsules, and Pills

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tablets
compressed
formulas
molded
capsules
hard gelatin
soft gelatin
pills
other solid
dosage forms

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 non-solvated, 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. It is in this area 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, processing equipment, packaging, and the controls used during and after preparation (Fig. 89-1).

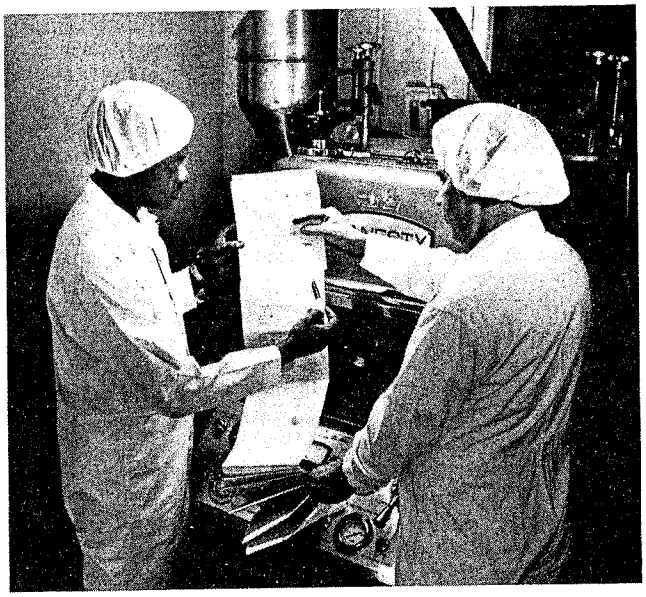


Fig. 89-1. Tablet press operators checking batch record in conformance with Current Good Manufacturing Practices (courtesy, Lilly).

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 (e.g., simplicity and economy of preparation, stability, and convenience in packaging, shipping, and dispensing) and the patient (e.g., 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.[2-6]

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, disintegrators, 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.

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, i.e., 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.

Prolonged-Action 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 tablets which continuously release increments of the contained drug substance to the gastrointestinal fluids. These tablets are discussed in Chapter 91.

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.

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

Buccal and Sublingual Tablets—These are small, flat, oval tablets. Tablets intended for buccal administration by inserting into the buccal pouch dissolve or erode slowly. 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. 89-2. 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.

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, 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 com-

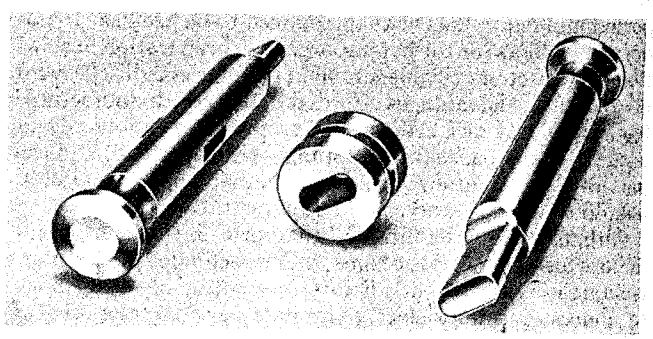


Fig. 89-2. Basic mechanical unit for tablet compression: lower punch, die, and upper punch (courtesy, Vector/Colton).

mercial 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.[7,8] See Chapters 37, 75 and 76.

Tablet Ingredients

In addition to the active or therapeutic ingredient, tablets contain a number of inert materials. The latter are known as additives or "adds." They may be classified according to the part they play in the finished tablet. The first group contains those which help to impart satisfactory compression characteristics to the formulation. These include (1) diluents, (2) binders, and (3) lubricants. The second group of added substances helps to give additional desirable physical characteristics to the finished tablet. Included in this group are (1) disintegrators, (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, 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. 1563.

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, e.g., 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 and starch, 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.

The direct compression method for preparing tablets (see page 1563) requires a material that not only is free-flowing but also sufficiently cohesive to act as a binder. This use has been described for a number of materials including microcrystalline cellulose, microcrystalline dextrose, amylose, and polyvinylpyrrolidone. It has been postulated that microcrystalline cellulose is a special form of cellulose fibril in which the individual crystallites are held together largely by hydrogen bonding. The disintegration of tablets containing the cellulose occurs by breaking the intercrystallite bonds by the disintegrating medium.

Starch Paste—Corn starch is 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.

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 improve the rate of flow of the tablet granulation, prevent adhesion of the tablet material to the surface of the dies and punches, reduce interparticle friction, and facilitate the ejection of the tablets from the die cavity. 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 be tableted tends to stick to the punches and dies. Immediately after compression most tablets have the tendency to expand and will bind and stick to the side of the die. The choice of the proper lubricant 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 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 coat the individual granules without breaking them down to finer particles. Prolonged blending of lubricant with a granulation can materially affect the hardness and disintegration time for the resultant tablets. The quantity of lubricant varies, being as low as 0.1%, and in some cases as high as 5%. Lubricants have been added to the granulating agents in the form of suspensions or emulsions. This technique serves to reduce the number of operational procedures and thus reduce the processing time.

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

The primary problem in the preparation of a water-soluble tablet is the selection of a satisfactory lubricant. Soluble lubricants reported to be effective include sodium benzoate, a mixture of sodium benzoate and sodium acetate, sodium chloride, leucine, and Carbowax 4000. However, it has been suggested that formulations used to prepare water-soluble tablets may represent a number of compromises between compression efficiency and water solubility. While magnesium stearate is one of the most widely used lubricants, its waterproofing 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.

Disintegrators

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

The most popular disintegrators 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. Starch pastes which are useful as binding agents will generally not be effective as disintegrating agents.

In addition to the starches a large variety of materials have been used and are reported to be effective as disintegrators. 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 granula-

tion, 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 disintegrators 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.

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. Colorimetric methods for testing color stability of tablets has been described. One method utilizing an instrument called a fadeometer gives results on color stability within 24 hours.[9]

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, e.g., 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. Among the most promising are two derivatives of glycyrrhizin, the glycoside obtained from licorice.[10] These derivatives are ammoniated glycyrrhizin and monoammonium glycyrrhizinate. The former is among the sweetest compounds on the FDA listing of natural GRAS flavors, its magnitude of sweetness being 50 times that of sucrose. Chemically, ammonium glycyrrhizin is the fully ammoniated product while monoammonium glycyrrhizinate is only partially ammoniated. The former is water-soluble, precipitating at pH 4.5 and lower while the latter exhibits poor solubility in water. 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, and disintegration time. 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. 89-17 and 89-18). 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. 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. See Fig. 89-3.

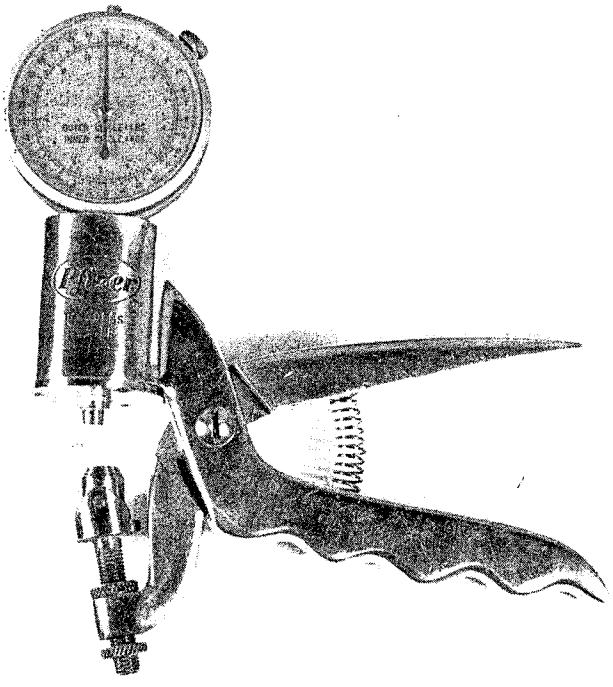


Fig. 89-3. The Pfizer tablet hardness tester (courtesy, Pfizer).

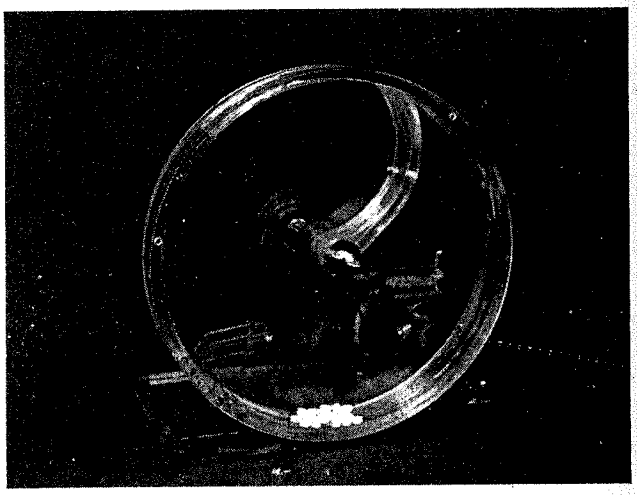


Fig. 89-4. The Roche friabilator (courtesy, Hoffmann-LaRoche).

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; if it is too soft, it will not withstand the handling during packaging and shipping operations.

Another approach to the measurement of tablet hardness is the 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. 89-4).

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 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.

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 to insure that proper-weight tablets are being made. The USP has provided tolerances for the average weight of uncoated compressed tablets. 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 US Pharmacopeia includes the content uniformity test. 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 a 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 a comparison of disintegration times and dissolution rates or initial absorption rates of several brands of aspirin tablets, it was found that the faster absorbed tablets had the longer disintegration time. Regardless of the lack of significance as to *in vivo* action of the tablets, the test provides a means of control in assuring that a given tablet formula is the same as regards disintegration from one production batch to another. The disintegration test is used as a control for tablets intended to be administered by mouth, except where tablets are intended to be chewed before being swallowed or where tablets are designed to release the drug substance over a period of time.

Exact specifications are given for the test apparatus inasmuch as a change in the apparatus can cause a change in the results of the test. The apparatus consists of a basket rack

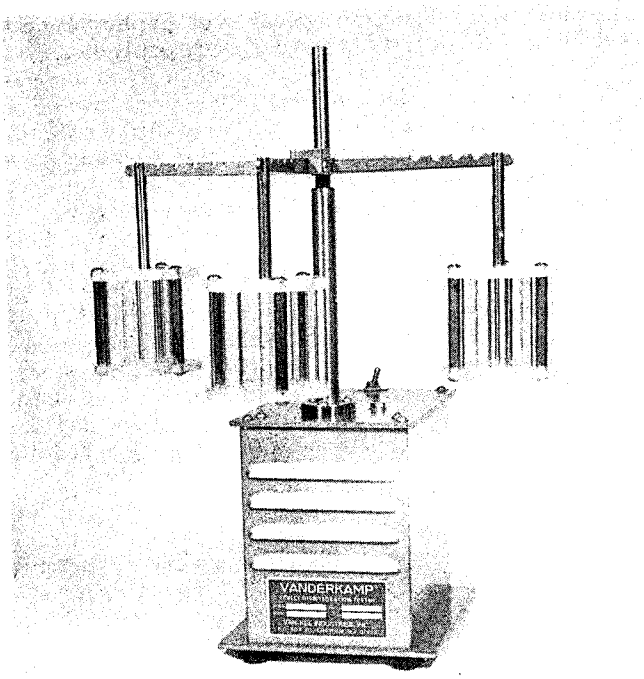


Fig. 89-5. Vanderkamp Tablet Disintegration Tester (courtesy, VanKel).

holding six plastic tubes, open at the top and bottom; the bottom of the tubes is covered with 10-mesh screen. See Fig. 89-5. The basket rack is immersed in a bath of suitable liquid, held at 37°C, preferably in a 1-liter beaker. The rack moves up and down in the fluid at a specified rate. The volume of the fluid is such that on the upward stroke the wire mesh remains at least 2.5 cm below the surface of the fluid and descends to not less than 2.5 cm from the bottom on the downward stroke. Tablets are placed in each of the six cylinders along with a plastic disk over the tablet unless otherwise directed in the monograph. The plastic disks have a density which enables them to float above the tablets. The end point of the test is indicated when the tablets have passed through the screen. 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°C, 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 effectiveness 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, it 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. The tablets for which a compendial dissolution requirement is provided include the following: Acetohexamide, Digitoxin, Digoxin, Hydrochlorothiazide, Meprobamate, Methandrostenolone, Methylprednisolone, Nitrofurantoin, Prednisolone, Prednisone, Quinidine Sulfate, Sulfamethoxazole, and the tablet containing the combination of theophylline, ephedrine hydrochloride, and phenobarbital.

Many procedures have been proposed for determining the dissolution rates of active substances from solid dosage forms. Three types of apparatus are officially recognized: Apparatus 1 (USP basket method), Apparatus 2 (USP paddle method), and Apparatus 3 (modified disintegration equipment method). The basket method is preferred by the USP unless otherwise indicated in the monograph. The suitability of a given apparatus for the dissolution test is determined by individually testing one tablet of the USP Dissolution Calibrator, Disintegrating Type (a prednisone tablet), and one tablet of the USP Dissolution Calibrator, Nondisintegrating Type (a salicylic acid tablet). The given type of apparatus is suitable if the results obtained with each tablet are within the stated acceptable range for that calibrator in the apparatus tested.

Apparatus 1 consists of a 40-mesh stainless steel basket placed on the end of the stirring shaft of a variable speed motor. The basket containing the tablet or capsule is immersed in the dissolution fluid designated and rotated at a speed indicated in the monograph. The dissolution fluid specified in the monograph could be one of the following: water, buffer solution, or dilute hydrochloric acid solution. The dissolution fluid is maintained at the temperature of 37°C and the volume of the fluid kept constant by adding a volume equal to that removed for sampling purposes. Samples of the fluid are removed at designated intervals and analyzed (see Fig. 89-6).

The apparatus for the paddle method includes a round bottom, 1000-ml container which can be placed in a constant temperature bath to hold the dissolution fluid at 37°C (see Fig. 89-6). The cover for the container has three ports providing openings for the stirring shaft, thermometer, and one for the removal of samples and replacement of dissolution fluid. The stirring shaft, attached to a varying speed motor, has a blade (paddle) held in a horizontal position near the bottom of the container. The tablet is dropped into the designated fluid through one of the ports and stirred at the rate indicated in the monograph. Samples are withdrawn and analyzed at indicated intervals. Both procedures allow for manual or automated timed-sample removal and testing. The automated procedure is helpful in controlling high-volume products.

Apparatus 3 consists of a modified USP disintegration apparatus. For the dissolution application no plastic disks are used; the bottom of the basket-rack assembly descends to 1 cm from the inside bottom surface of the vessel on the downward stroke; the 10-mesh stainless steel cloth in the basket-rack assembly is replaced with 40-mesh stainless steel cloth; and the 40-mesh stainless steel cloth is fitted to the top of the basket-rack assembly to prevent the solid dosage form from floating out of the assembly's plastic tubes.

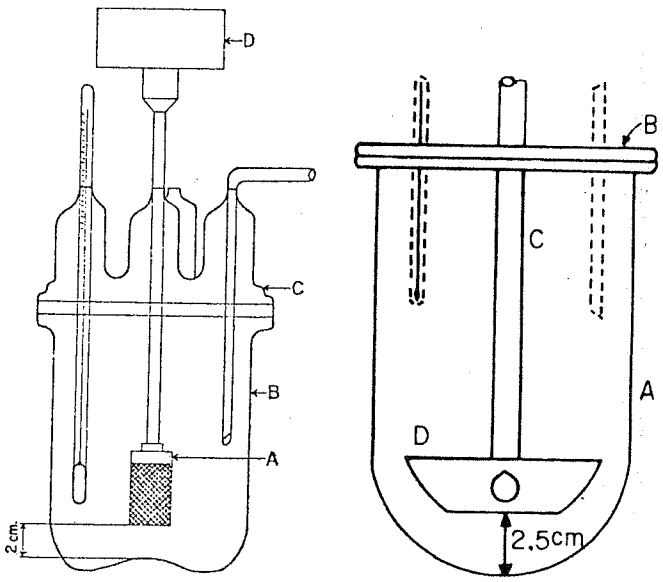


Fig. 89-6. Apparatus 1: A—rotating basket assembly; B—container for dissolution fluid; C—4-hole cover for container; D—varying speed stirring motor.

Apparatus 2: A—container for dissolution fluid; B—3-hole cover for container; C—stirring shaft attached to varying speed motor; D—stirring blade (paddle) held in horizontal position.

Details of the interpretation of dissolution test results are provided in the USP.

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

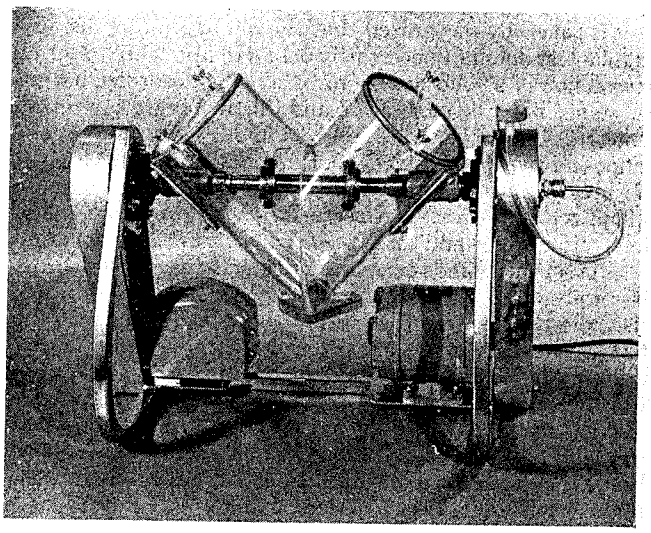


Fig. 89-7. Twin-shell blender for solids or liquid–solids blending (courtesy, Patterson-Kelley).

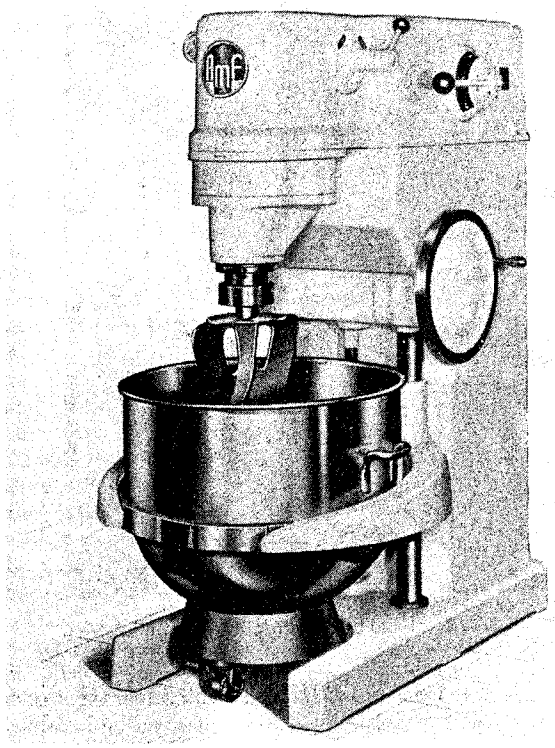


Fig. 89-8. The Glen powder mixer (courtesy, Am. Machine).

depends on the quantity or size of the batch. The active ingredient, diluent, and disintegrator 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. 89-7). Twin-shell blenders are available in many sizes from laboratory models to large production models. Blenders of the vertical shift type, e.g., the Glen mixer and the Hobart mixer, have served this function in the pharmaceutical industry for many years (Fig. 89-8). On a large scale, ribbon blenders are also frequently employed and may be adapted for continuous production procedures.

Solutions of the binding agent are added to the mixed powders with stirring. The powder mass is wetted with the binding solution until the mass has the consistency of damp snow or brown sugar. If the granulation is overwetted, the granules will be hard, requiring considerable pressure to form the tablets, and the resultant tablets may have a mottled appearance. If the powder mixture is not wetted sufficiently, the resulting granules will be too soft, breaking down during lubrication and causing difficulty during compression. For larger quantities mass mixers of the sigma-blade type have been widely used in the pharmaceutical industry (Fig. 89-9). Twin-shell blenders are also constructed to permit the binding solution to be sprayed on the powder blend for granulation following the mixing operation.

The wet granulation is forced through a 6- or 8-mesh screen.

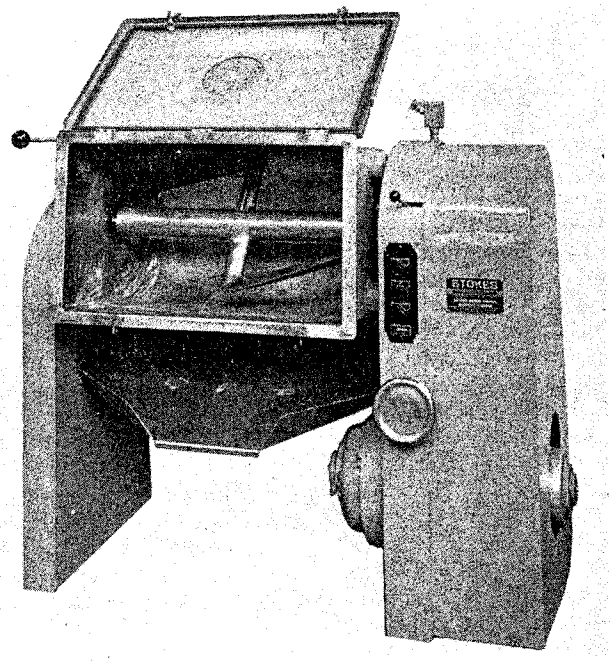


Fig. 89-9. Mass mixer for granulations (courtesy, Stokes).

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. 89-10. In addition to the comminuting mills in which the granulation is forced through the sieving device by rotating hammers, knives, or oscillating bars, a Swiss milling machine called the Artofex (*Excelsior*) cylindrical shredder is being used. The milling chamber consists of a rotating shredding drum into

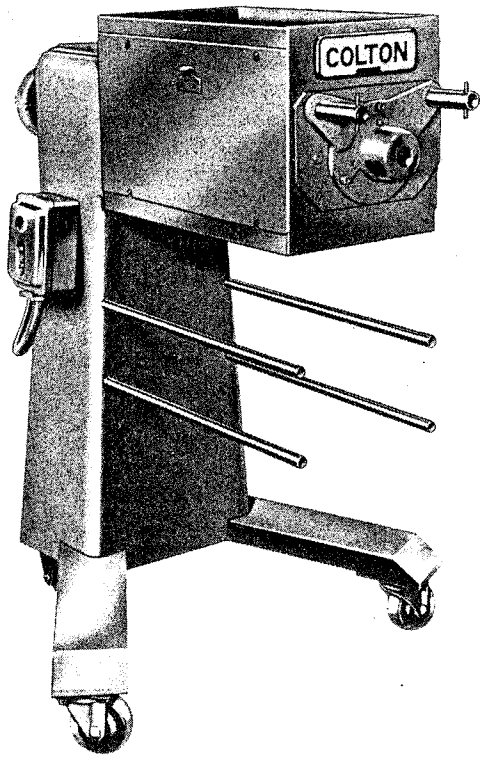


Fig. 89-10. Rotary granulator and sifter (courtesy, Vector/Colton).

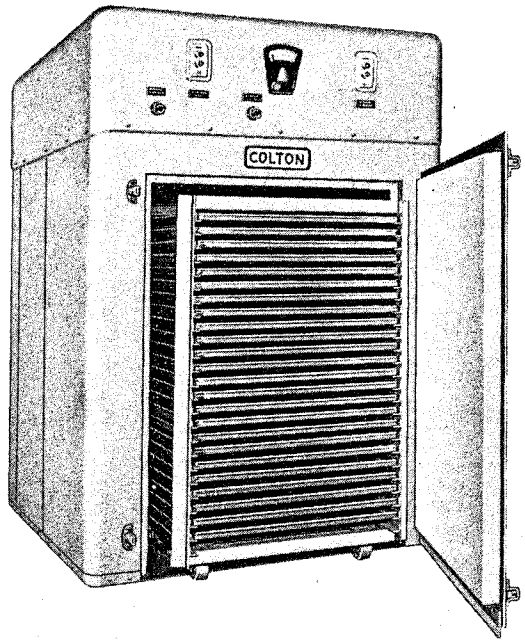


Fig. 89-11. Tray dryer oven (courtesy, Vector/Colton).

which the material flows and is sheared against the sides of the drum by impellor blades rotating at a higher speed. This action plus centrifugal force results in the formation of distinct granules. Although it can be used for either wet or dry granulations, the significant advantage claimed is its ability to granulate efficiently extremely wet masses.

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 granulator 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 Figs. 89-11 and 89-12. While tray drying is the most widely used method of drying tablet granulations, other methods are being introduced with success. Notable among these are the fluid-bed dryers. In drying tablet granulations 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

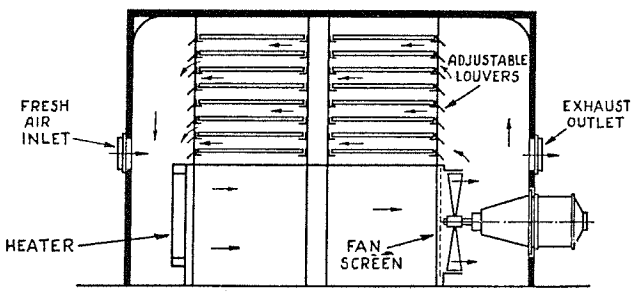


Fig. 89-12. Cross section of tray dryer.

Fig. 89-13. Fluid bed dryer (courtesy, Stokes).

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. 89-13.

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 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 wooden block. 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 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.[11] 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. 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 1587). Methods for the preparation of compressed tablets have been reviewed in the literature.[12]

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. 89-14.

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; 7/8 to 1 in. are the most practical sizes for slugs. Sometimes, to obtain the pressure which is desired the slug sizes are reduced to 3/4 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*) 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. Also, this method should produce tablets of faster dissolution rates because no colloidal binders such as gelatin or starch are used to surround the granules. Approaches being used to make this method more universally applicable include the introduction of formulation additives capable of imparting the

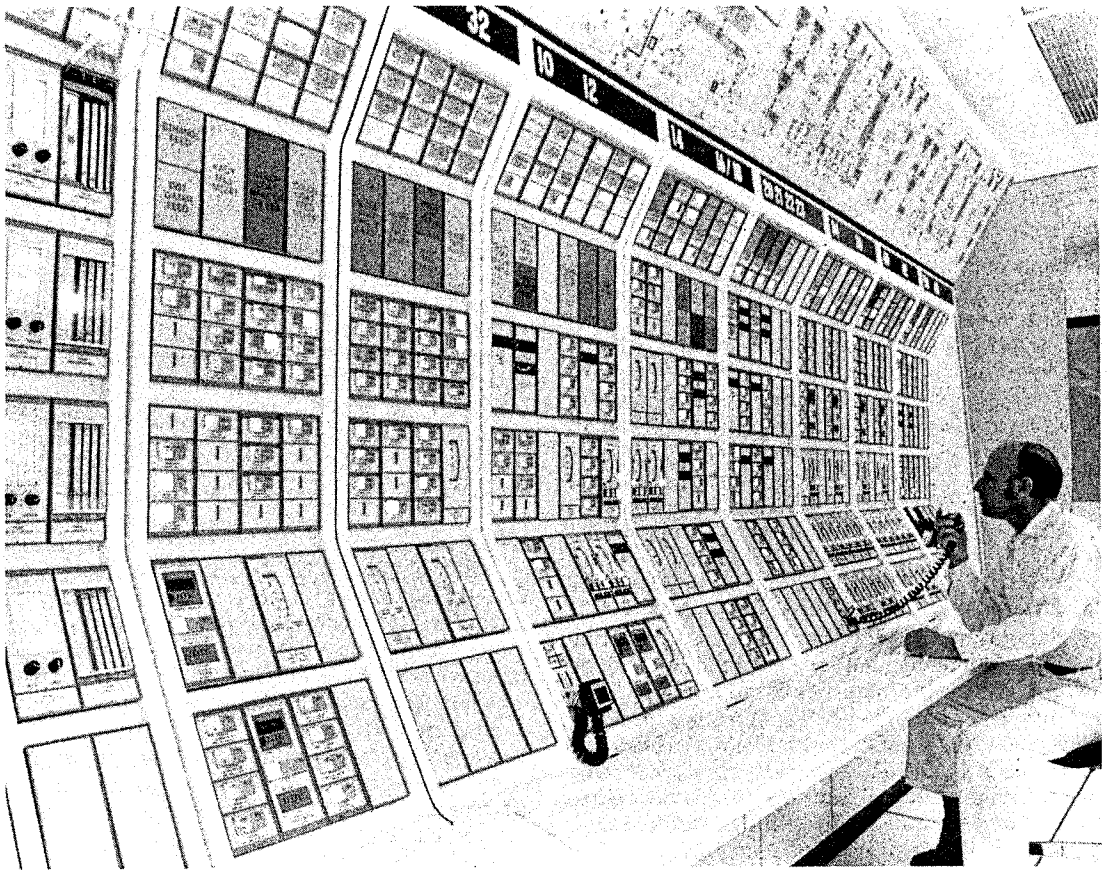


Fig. 89-14. Computer control room for the first large-scale computer-controlled tablet manufacturing facility (courtesy, MSD).

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.[13]

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 dicalcium phosphate dihydrate, compressible sugar, lactose, mannitol, and microcrystalline cellulose. Dicalcium phosphate dihydrate (*Di-Cal,* 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.

Other additives used in direct-compression formulas include cellulose [*Solka-Floc* (Brown)] and colloidal silica, such as *Cab-O-Sil* (Cabot) or *Quso* (Phila. Quartz). Silica acts as a glidant in promoting flowability of the granulation.

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. 89-28.

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 1572.

Related Granulation Processes

Spheronization—Spheronization, a form of pelletization, refers to the formation of spherical particles from wet granulations. Since the particles are round, they have good flow properties when dried. They can be formulated to contain sufficient binder to impart cohesiveness for tableting. Spheronization equipment called the Marumerizer machine (*Elanco*) 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 screen (see Fig. 89-15). The pellets are then dried by conventional methods, mixed with suitable lubricants, and compressed into tablets. Microcrystalline cellulose has been shown to be an effective binder in granulations to be spheronized.[14,15] The advantages of the process include the production of granules, regular in shape, size, and surface characteristics; low friability resulting in fewer fines; and the ability to regulate the size of the spheres.

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. 89-16, the feed is sprayed into a current of warm filtered air. The air supplies the heat 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.[16]

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.

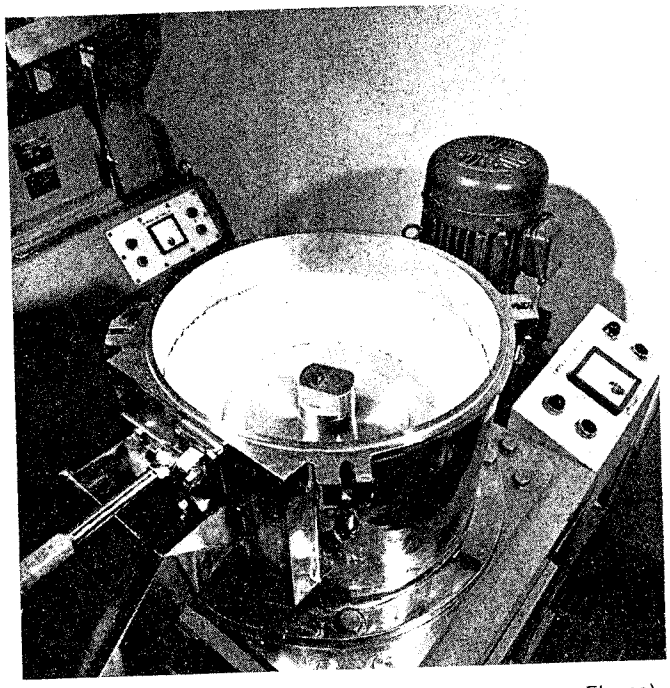


Fig. 89-15. The inside of a Q-400 Marumerizer (courtesy, Elanco).

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

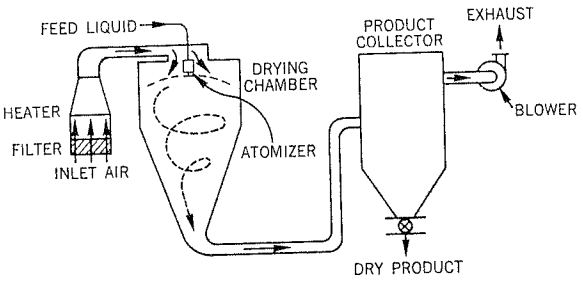


Fig. 89-16. Typical spray-drying system (courtesy, Bowen Eng.).

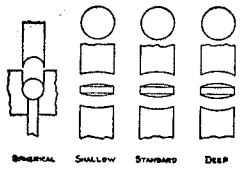


Fig. 89-17. Concave punches.

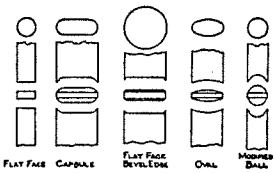


Fig. 89-18. Specially shaped punches.

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°C 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. 89-17 and 89-18. 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: $\frac{3}{16}$ in., $\frac{7}{32}$ in., $\frac{1}{4}$ in., $\frac{9}{32}$ in., $\frac{5}{16}$ in., $\frac{11}{32}$ in., $\frac{7}{16}$ in., $\frac{1}{2}$ in., $\frac{9}{16}$ in., $\frac{5}{8}$ in., $\frac{11}{16}$ in., and $\frac{3}{4}$ 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[17] 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. 89-19 and Fig. 89-20. 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.

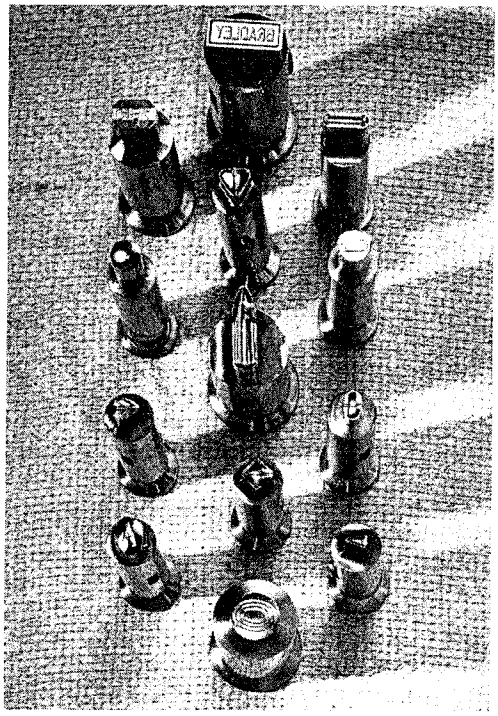


Fig. 89-19. Collection of punches (courtesy, Stokes).

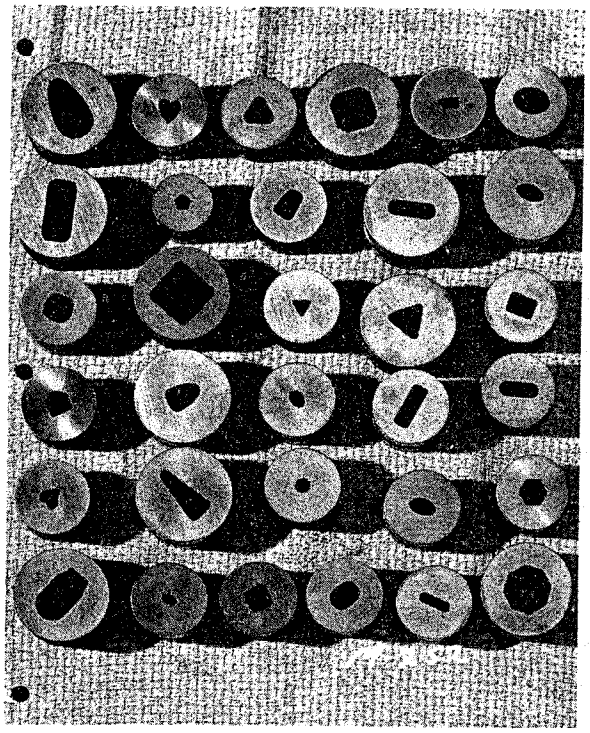


Fig. 89-20. Collection of dies (courtesy, Stokes).

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.[18]

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

Table I—Single-Punch Tablet Machines

Machine model	Maximum tablet diameter (in.)	Press speed (tablets/min)	Depth of fill (in.)
Key Industries equipment			
Eureka	1/2	75	7/16
Stokes equipment[a]			
511-5	1/2	40–75	7/16
519-2	3/4	60–95	11/16
521-2	1 1/4	25–55	1 1/4
530-1	2	12–48	1 5/8
525-2	3	16–48	2
Manesty equipment (Thomas Eng.)			
Hand machine	1/2	100	7/16
Model F3	7/8	85	11/16
Model 35T[a]	3	36	2 1/4
Kilian equipment (Key Ind.)[a]	(mm)		(mm)
KS	18	25–80	16
KIS	35	25–50	21
KII	60	8–33	60

[a] Widely used for veterinary boluses.

is one of the causes of capping. This is especially necessary to observe in the case of deep-cup punches.

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

Single-Punch Machines

The simplest tableting machines available are those having the single-punch design. A number of models are available as outlined in Table 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. 89-21 and Fig. 89-22. 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 1/2 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.

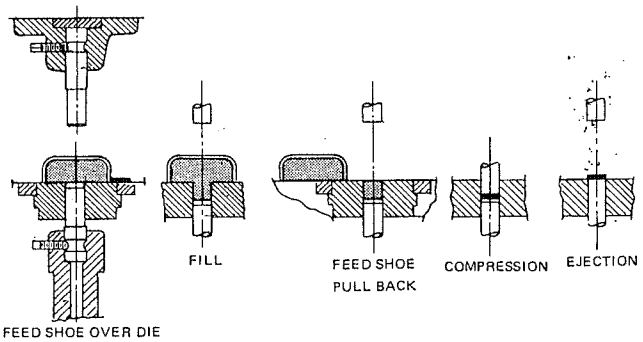


Fig. 89-21. Formation of tablet on single-punch machine (courtesy, Vector/Colton).

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 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.

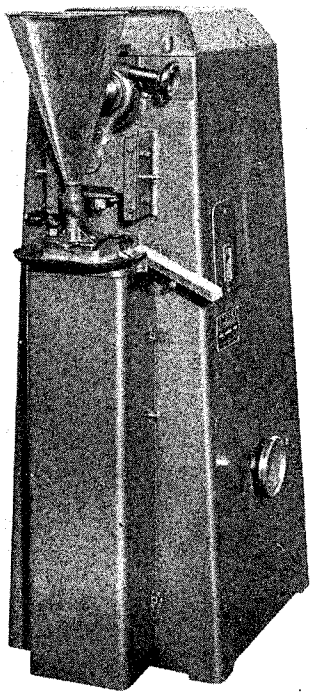


Fig. 89-22. Model F, heavy-duty single-punch machine for tablets requiring heavy pressure (courtesy, Stokes).

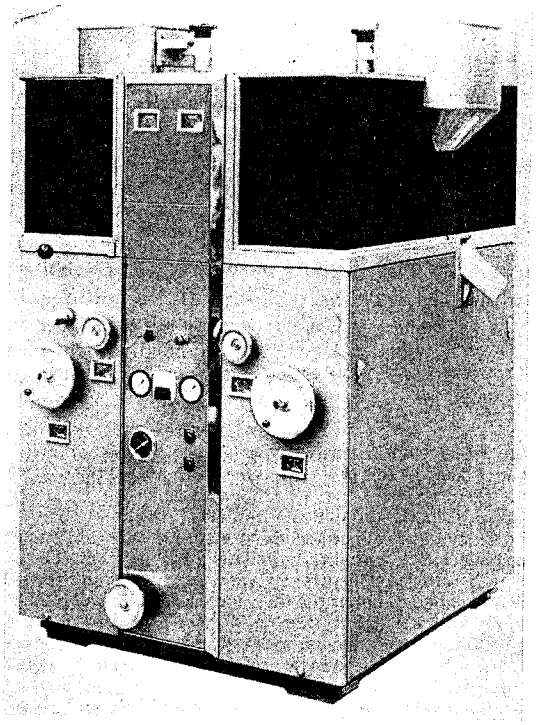


Fig. 89-23. Model 610, GTP Press, double-sided rotary compacting press designed to produce at speeds over 10,000 tablets/min (courtesy, Stokes).

Rotary Tablet Machines

For increased production rotary machines (Fig. 89-23) offer great advantages. A head carrying a number of sets of punches and dies revolves continuously while the tablet granulation runs from the hopper, through a feed frame, and into the dies placed in a large, steel plate revolving under it. This method promotes a uniform fill of the die and therefore an accurate weight for the tablet. Compression takes place as the upper and lower punches pass between a pair of rollers. 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. 89-24 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.

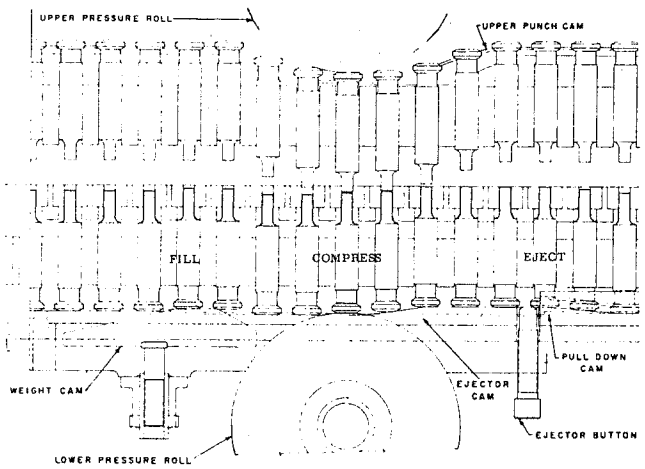


Fig. 89-24. Tooling for a 16-station rotary press showing positions of the cycle required to produce 1 tablet/set of tooling (courtesy, Vector/Colton).

Table II—Rotary Tablet Machines

Machine model	Tool sets	Maximum tablet diameter (in.)	Press speed (tablets/min)	Depth of fill (in.)
Vector-Colton equipment				
216	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	18	2	325	2 3/4
	25	1 3/8	450	2 3/4
Stokes equipment				
512-1	16	5/8	350–1050	11/16
515-1	15	1 3/16	180–335	1 1/16
515-3	15	1 3/16	180–335	1 9/16
516-1	23	1 3/16	240–720	1 3/8
517-1	23	1 3/16	120–360	2 1/16
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
RS3	14	2 3/4	84–224	2 1/2
	16	2 1/2	96–256	2 1/2
	20	1 15/16	126–336	2 1/2
Fette equipment (Raymond Auto.)				
		(mm)		(mm)
Perfecta 1000	22	35	1210	22
	28	16	2100	18
	33	13	2475	18
Perfecta 2000	29	25	2175	22
	36	16	3600	18
	43	13	4300	18
Kilian equipment (Key Ind.)				
		(mm)		(mm)
Pharma RLA-20	20	13	550–1580	16
Eifel 24A-III	24	16	650–1750	15–20
RT-228-A	28	13	1000–3000	15–20
NRD 51-A	51	13	2600–7500	15–20
Prescoter	20	20	230–660	16
DPID	41	20	550–1100	20–38

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

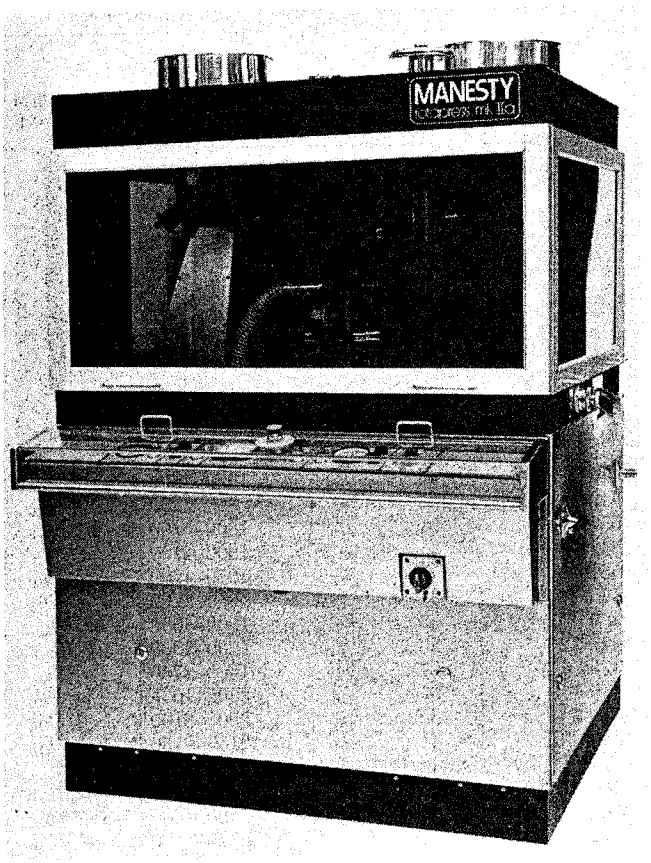


Fig. 89-25. Rotapress Mark IIA; designed for improvements in sound reduction, operator safety, cleanliness, and operational convenience; note control panel on front of machine (courtesy, Thomas/Manesty).

bore coincides with the plug hole. Insert each lower punch in its place progressively. Insert the upper punches by dropping them into place in the head. Each punch (upper and lower) should be coated with a thin film of mineral oil before inserting them into the machine. Adjust the ejection cam so that the lower punch is flush with the die table at the ejection point.

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

Fill the hopper with the granulation and turn on the power. Check tablet weight and hardness immediately after the mechanical operation begins and make suitable adjustments, if necessary. Check these properties routinely and regularly at 15–30 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. 89-25 and 89-26. This has been accomplished by increasing the number of stations, i.e., 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. 89-27, the drawing shows a rotary

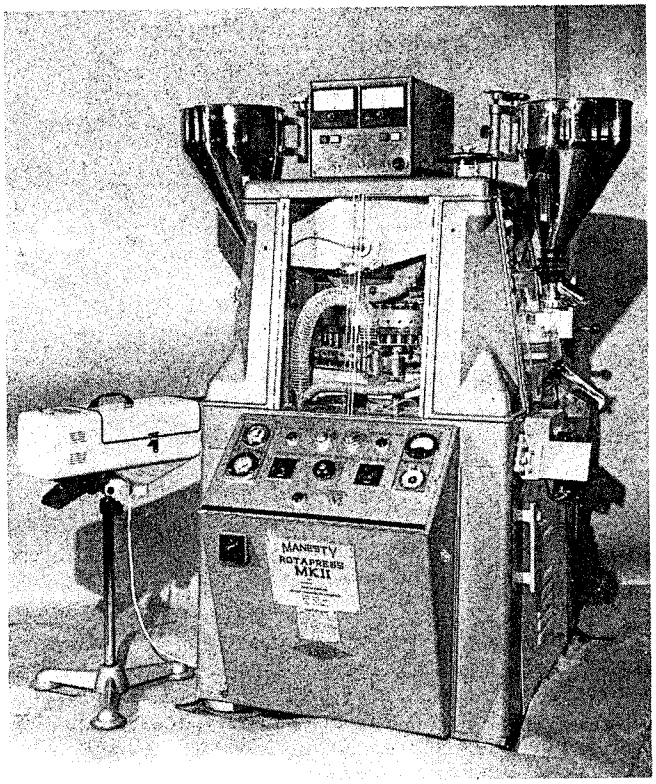


Fig. 89-26. Mark II Rotapress with 61 stations, equipped with deduster (left) and the Thomas Tablet Sentinel (top of press) (courtesy, Thomas/Manesty).

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. 89-28. Presses with triple compression points (see Table III)

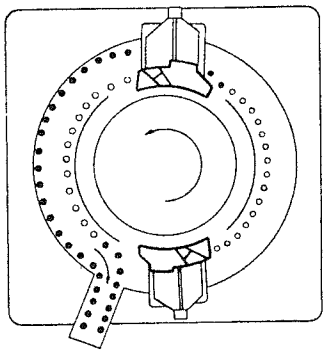


Fig. 89-27. The movement of tablets on die table of a double rotary press (courtesy, Vector/Colton).

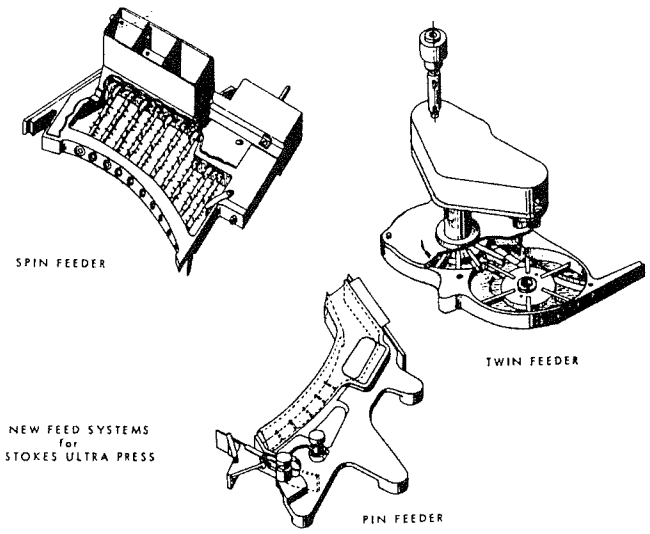


Fig. 89-28. Feeding devices designed to promote flow of granulations for high-speed machines (courtesy, Stokes).

permit the partial compaction of material before final compaction. This provides for the partial deaeration and particle orientation of material before final compression. This helps in the direct compacting of materials and reduces laminating and capping due to entrapped air.

Multilayer Rotary Tablet Machines

The rotary tablet machines also have been developed into models capable of producing multiple-layer tablets; the machines are able to make one-, two-, or three-layer tablets. 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.

Another development in the rotary compression machines has been the compression coating machines which are described in Chapter 90.

Capping and Splitting of Tablets

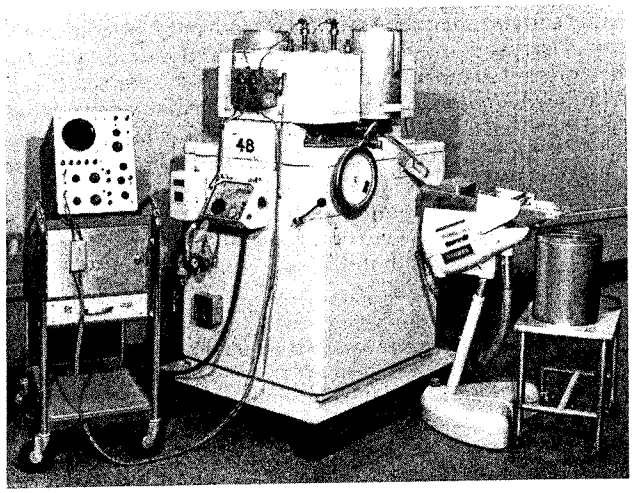
The splitting or capping of tablets is one of great concern and annoyance in tablet making. It is quite difficult to detect while the tablets are being processed but can be detected easily by vigorously shaking a few in the cupped hands. A slightly chipped tablet does not necessarily mean that the tablet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

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				
247	33	5/8	3480	3/4
	41	7/16	4300	3/4
	49	7/16	5150	3/4
1033	33	5/8	3480	3/4
1041	41	7/16	4300	3/4
1049	49	7/16	5150	3/4
Magna	46	17/32	6624	1 1/8
Magna	54	31/32	8640	3/4
Magna	66	23/32	10,560	3/4
Magna	74	1/2	11,840	3/4
Magna	90	7/16	14,400	3/4
Stokes equipment				
513-2	45	7/16	1050–4200	11/16
513-3	35	5/8	800–3200	11/16
551-1	51	7/16	1800–5100	11/16
541-1	41	5/8	1500–4100	11/16
551-1	45	7/16	1050–4200	11/16
555-2	35	5/8	800–3200	11/16
328-4	45	3/4	1600–4500	1 3/8
328-124	33	1 1/16	1200–3300	1 3/8
328	27	1 3/16	1000–2700	1 3/8
610-1	65	7/16	3500–10,000	11/16
610-2	53	5/8	2900–8100	11/16
610-3	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
552-1	51	7/16	2225–5100	11/16
552-2	41	5/8	1320–4100	11/16
610-4	65	7/16	3500–10,000	11/16
610-5	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
BB3B	35	5/8	1490–2980	11/16
	45	7/16	1913–3826	11/16
Rotapress Mark II	37	1	710–3550	13/16
	45	5/8	8182	11/16
	55	7/16	10,000	11/16
	61	7/16	11,100	11/16
Mark IIA	37	1	710–3550	13/16
	45	5/8	1640–8200	11/16
	55	7/16	2000–10,000	11/16
	61	7/16	2220–11,100	11/16
Rotapress Mark III	45	1	1504–3762	13/16
	55	5/8	8000	11/16
	75	7/16	10,869	11/16
Fette equipment (Raymond Auto.)		(mm)		(mm)
Perfecta 3000	37	25	4400	22
	45	16	6750	18
	55	13	10,500	18



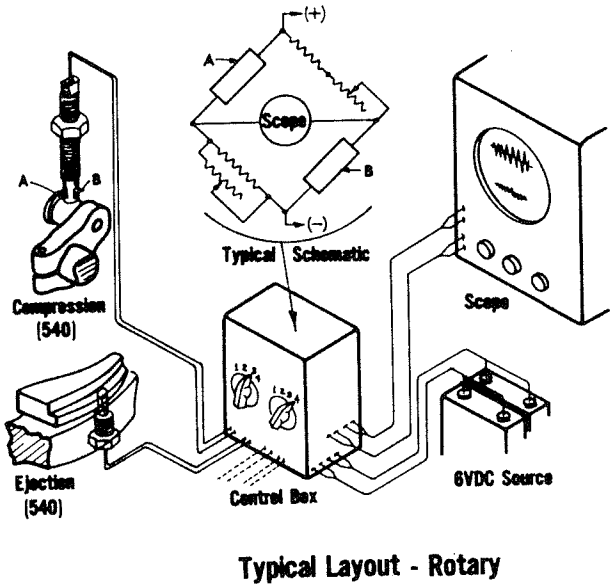


Fig. 89-29. Upper photo: High-speed rotary press equipped with strain gauges; Lower photo: layout showing arrangement of electronic components (courtesy, Upjohn).

punch out of alignment may cause one tablet to split or cap on every revolution.

Instrumented Tablet Presses

Compressional and ejectional forces involved in tablet compression can be studied by attaching strain gauges to the punches and other press components involved in compression. The electrical output of the gauges has been monitored by telemetry or use of a dual beam oscilloscope equipped with camera.[19,20] 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. 89-29).

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.*)] 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. 89-26).

Fig. 89-30. Fette Perfecta 3000 high-speed tablet press with pressing compartment completely sealed off from outside environment making cross contamination impossible (courtesy, Raymond Auto.).

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. 89-30, 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 1436).

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	43.25 mg	432.5 g

Blend acetaminophen, polyvinylpyrrolidone, and lactose together; pass through a 40-mesh screen. Add the alcohol slowly and knead well. Screen the wet mass through a 4-mesh screen. Dry 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	6.5 mg	45.5 g
Calcium stearate (impalpable powder)	1 mg	7 g
Weight of granulation		836.5 g

[a] Includes 10% in excess of claim.

Granulate the 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, $^{1}/_{4}$-in. punch. 20 tablets should weigh 2.39 g.

Chewable Antacid Tablets

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

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

CT Hexavitamin

Ingredients	In each	In 7000
Ascorbic Acid USP (powder)[a]	82.5 mg	577.5 g
Thiamine Mononitrate USP (powder)[a]	2.4 mg	16.8 g
Riboflavin[a]	3.3 mg	23.1 g
Nicotinamide USP (powder)[a]	22 mg	154 g
Starch	...	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 $^{1}/_{4}$-inch concave punch. 10 tablets should weigh 1.25 g.

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

Direct Compression 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] Reheis 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. 89-31). In some hand molds,

Fig. 89-31. Hand molding tablet triturates (courtesy, MSD).

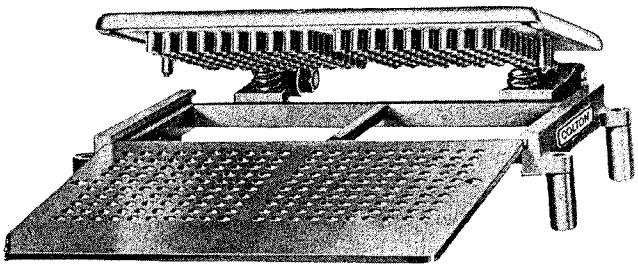


Fig. 89-32. Tablet triturate mold (courtesy, Vector/Colton).

as shown in Fig. 89-32, the pegs are forced down onto the plate holding the moist trituration.

Formulation

In developing a formula it is essential that the blank weight of the mold which is to be used is known. To determine this, the weight of the diluent which exactly fills all the openings in the mold is determined by experiment. This amount of diluent is weighed and placed aside. The total amount of the drug required is determined by multiplying the number of perforations in the plate used in the previous experiment by the amount of drug desired in each tablet. The comparative bulk of this medication is 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 88.

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 be placed with the remainder of the unmolded material.

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

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

Machine-Molding Tablet Triturates

Tablet triturates also can be made using mechanical equipment. The automatic tablet triturate machine illustrated in Fig. 89-33 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

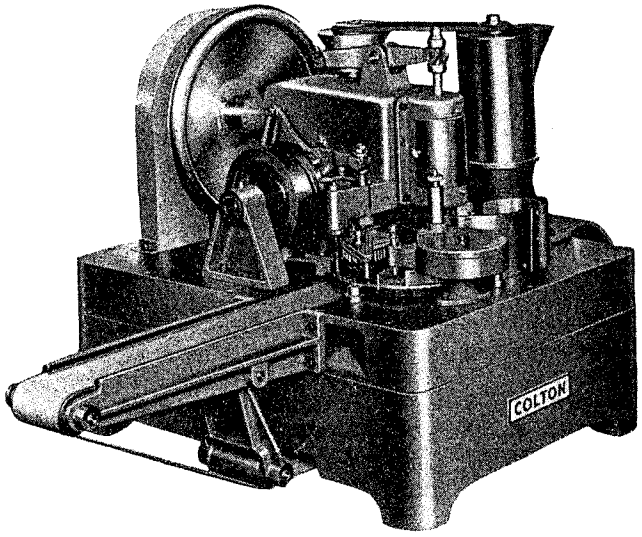


Fig. 89-33. Automatic tablet triturate machine (courtesy, Vector/Colton).

shorter. The moistened mass passes through the funnel of the hopper to the feed plates below. In this feed plate are four holes having the same diameter as the mouth of the funnel. The material fills one hole at a time and when filled 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.[21]

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.

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. Its shape is illustrated in Fig. 89-34. 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, 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. 89-35 and 89-36. These show the

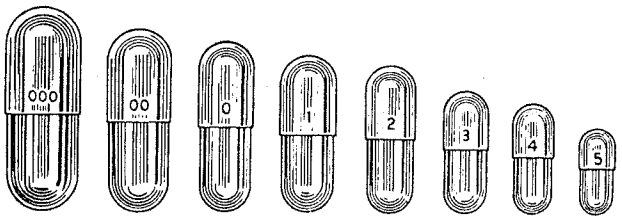


Fig. 89-34. Hard gelatin capsules showing relative sizes (courtesy, Parke-Davis).

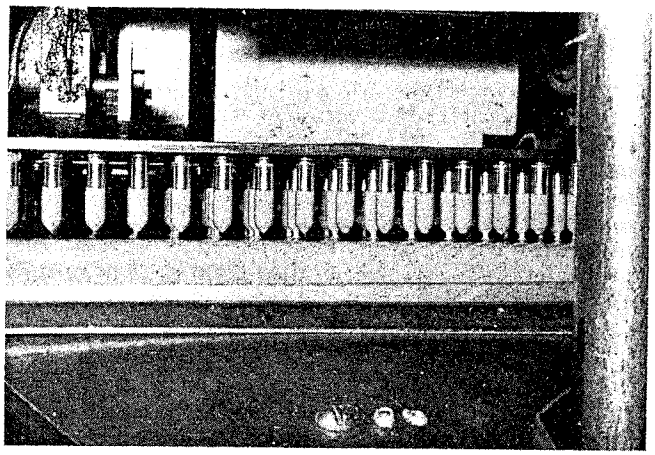


Fig. 89-35. Manufacturer of hard gelatin capsules by dipping stainless steel pins into gelatin solutions (courtesy, Lilly).

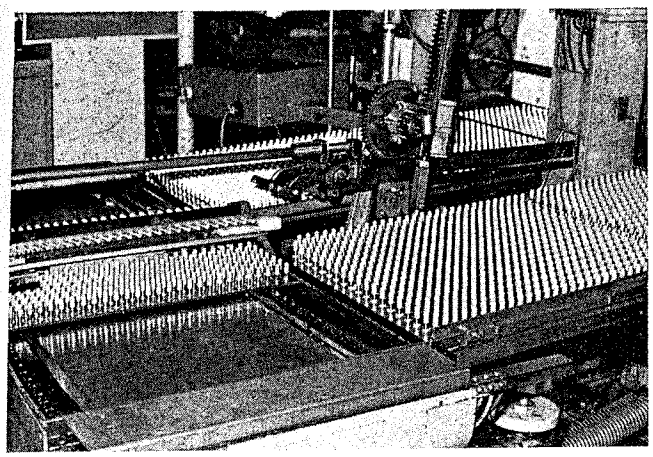


Fig. 89-36. Formed capsules being dried by rotating through drying kiln (courtesy, Lilly).

stainless steel pins being dipped into the gelatin solutions and then being rotated through the drying kiln.

Capsules are supplied in a variety of sizes. The hard, empty capsules (Fig. 89-34) 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* capsule. 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 88. 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. 89-37 illustrates a capsule filling ma-

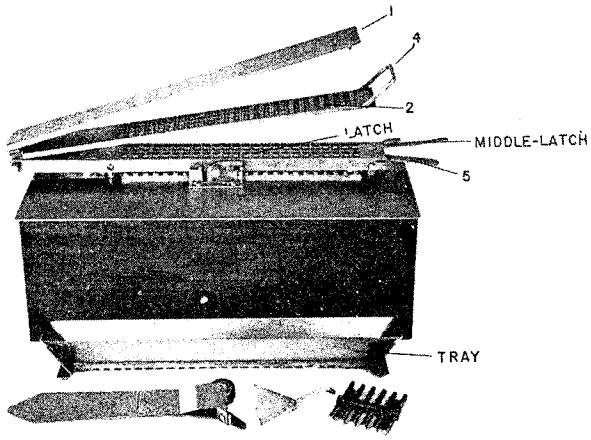


Fig. 89-37. Hand-operated capsule machine (courtesy, Chemi-Pharm).

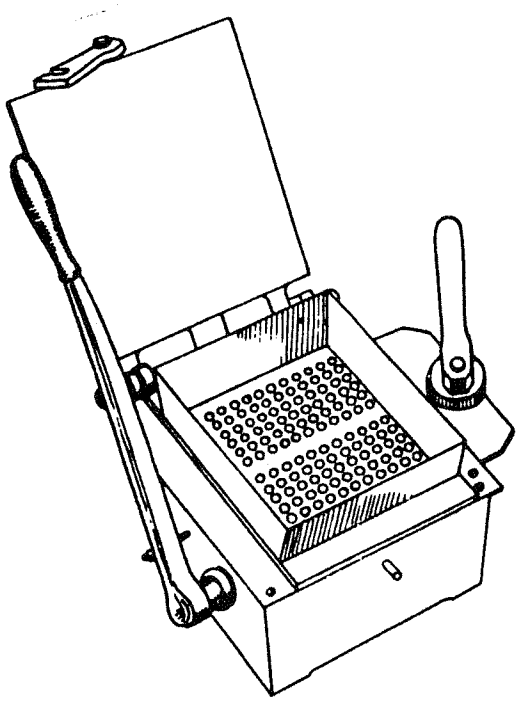


Fig. 89-38. Hand-operated capsule machine, Model 300 (courtesy, ChemiPharm).

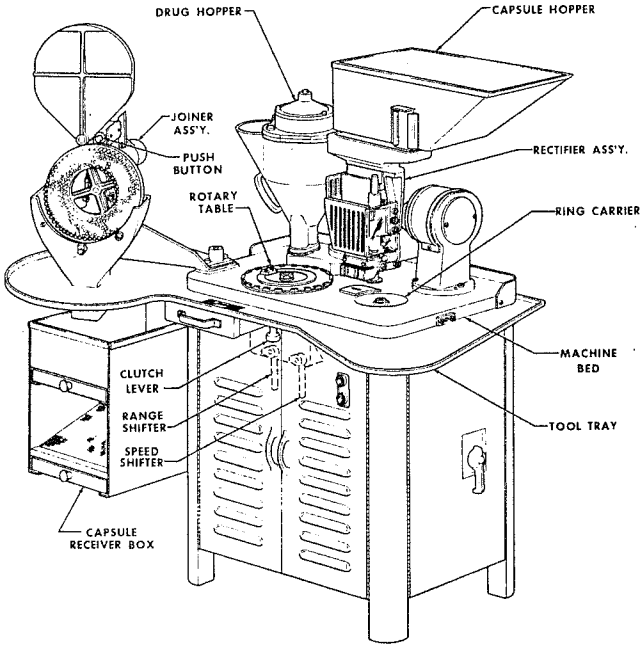


Fig. 89-39. Schematic of Type 8 capsule-filling machine (courtesy, Parke-Davis).

chine 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. 89-38 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.

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.

Semiautomatic capsule-filling machines manufactured by Parke-Davis and by Lilly are illustrated in Figs. 89-39 and 89-40. 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

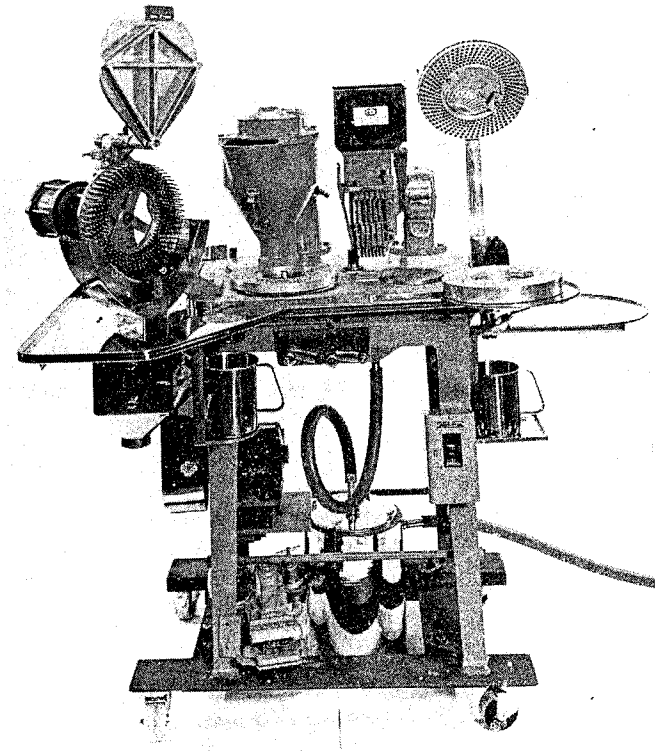


Fig. 89-40. Type 8 capsule-filling machine (courtesy, Lilly).

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.

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,

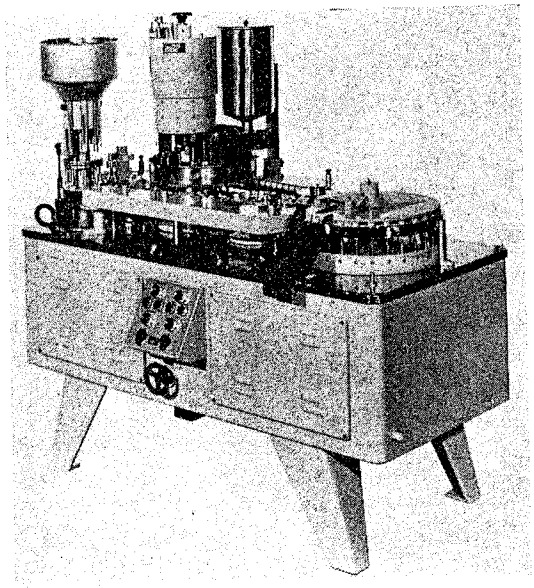


Fig. 89-41. MG-2, automatic capsule-filling machine (courtesy, Supermatic).

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. 89-41, 89-42, and 89-43).

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.

Weight Variation

Twenty intact hard gelatin capsules are weighed individually and the average weight is determined. The requirements are met if each of the individual weights are within 90–110% of the average weight. If this requirement is not met, then the weight of the contents for each individual capsule is

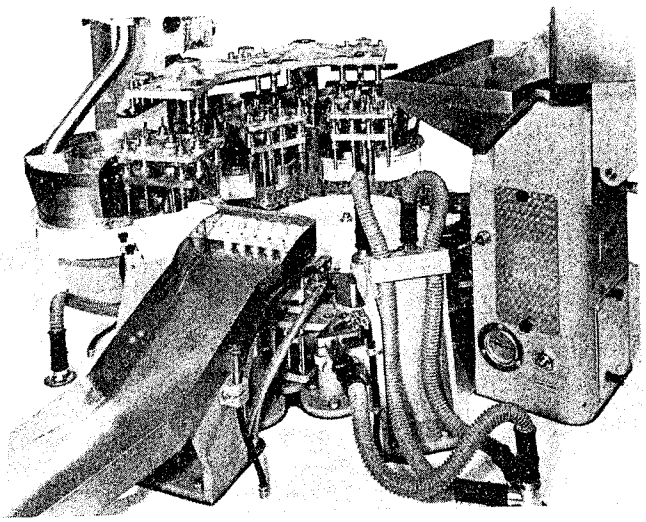


Fig. 89-42. Zanasi automatic filling machine, Model AZ-60. The set of filling heads shown at the left collects the powder from the hopper, compresses it into a soft slug, and inserts it into the bottom half of the capsule (courtesy, United Machinery).

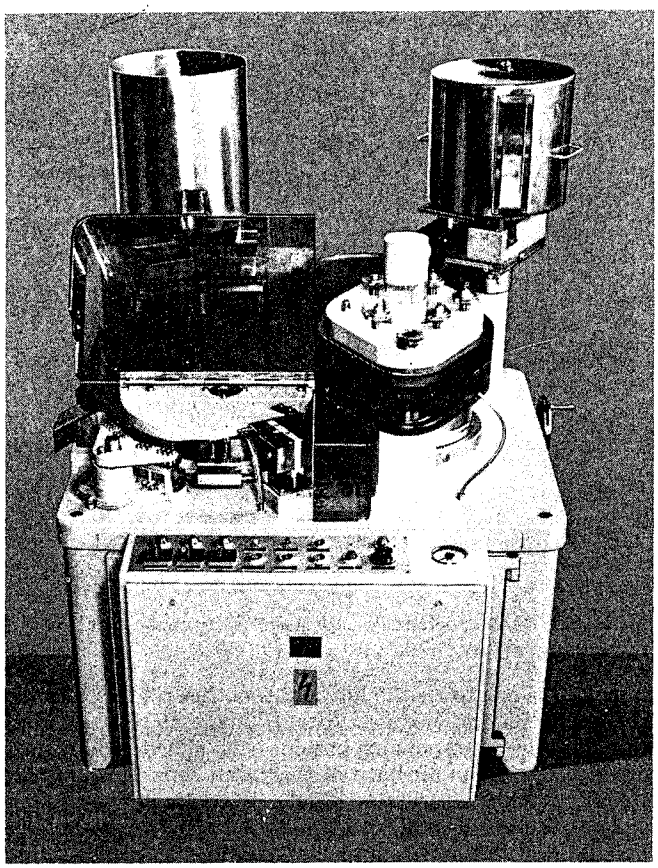


Fig. 89-43. Hoefliger & Karg automatic capsule filling machine, Model GFK 1200 (courtesy, Amaco).

determined and compared with the average weight of contents.

A similar procedure is followed for soft gelatin capsules. After the individual gross weights of the capsules are determined, the shells are carefully opened by cutting and the contents removed by washing with a suitable solvent. After the shells have dried, they are weighed and the content weights of the individual capsules are calculated. See the compendia for details of the procedure.

Content Uniformity

This requirement is comparable to the one for compressed tablets. It is applicable to 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. An exception is made in those cases where the assay method proves impracticable for the accurate determination of the drug content of individual dosage units. For some capsules a separate assay method is included for the content uniformity test and is referred to as Method II. The official compendium can be consulted for the details of the test. Capsule monographs with a content uniformity requirement do not have a weight variation requirement.

Capsule Disintegration

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.

Dissolution Test

For certain capsule dosage forms, such as those containing chlordiazepoxide, indomethacin, quinidine sulfate, or thiothixene, a dissolution requirement is part of the monograph. Procedures used are similar to those employed in the case of compressed tablets.

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. 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 may be elliptical, oblong, or round in shape. 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.

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.

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

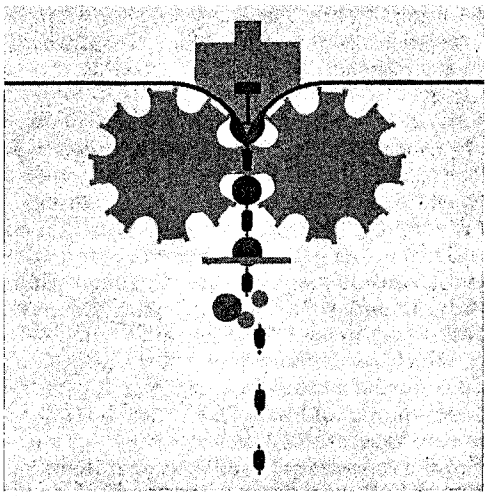


Fig. 89-44. Rotary die elastic capsule filler.

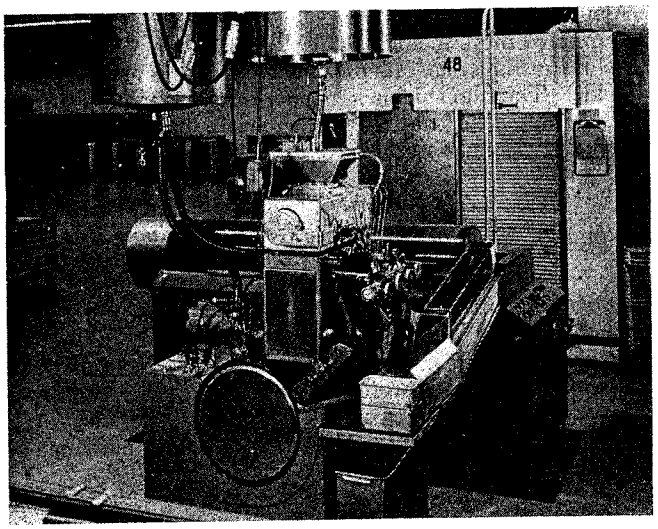


Fig. 89-45. Scherer soft elastic capsule machine (courtesy, Scherer).

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. 89-44. See also Fig. 89-45.

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

The most recent and major advance in pharmaceutical capsule manufacture was made in 1948 when the Accogel machine and process 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 micron to 5000 μ 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.

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) rig-

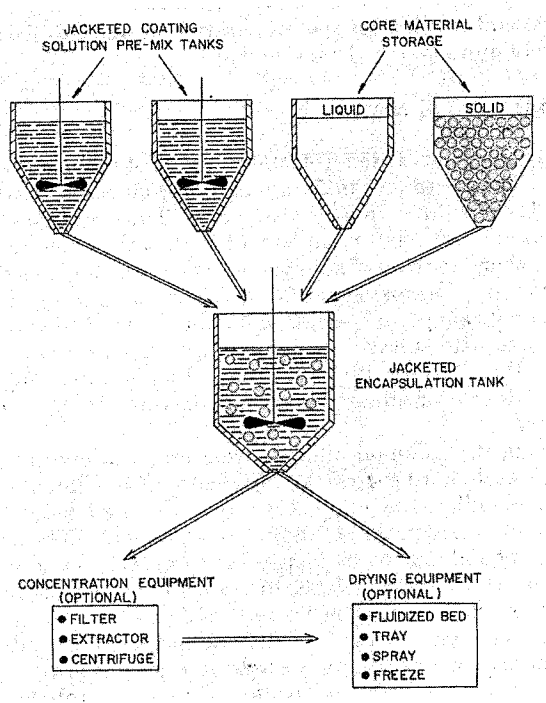


Fig. 89-46. Production installation for microencapsulation process (courtesy, NCR).

idizing 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. 89-46 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.

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, 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 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 given below does not apply to hexylresorcinol pills.

Preparation of Mass

In preparing pills the first step consists of making the pill mass. The ingredients in the pill mass include the active drug, the diluent or filler, and the excipient. The selection of the diluent and excipient is important in that they give the essential characteristics of adhesiveness, firmness, and plasticity to the mass. The mass must be sufficiently adhesive and firm to retain its shape, yet be soft enough to be worked with the fingers, or with suitable equipment, into the desired pilular form. Plasticity results when the pill mass possessing the proper degree of adhesiveness and firmness is thoroughly kneaded.

Among the common diluents used are powdered glycyrrhiza, starch, hard soap, and tragacanth. The diluent gives increased bulk to the pill mass; the quantity used depends on the quantity and nature of the active ingredient. The active ingredient and diluent are blended and the excipient is added to form a cohesive mass. The quality of the finished pill depends on the selection of the excipient in relation to the physical characteristics of the diluent and active ingredient. Commonly used excipients include glucose, glycerin, acacia mucilage, simple syrup, and water. Glucose is probably the closest to an ideal excipient. It is colorless, very adhesive, and maintains the pills in a soft, plastic condition. Pills in which acacia mucilage has been used as the excipient frequently harden with time.

The ingredients of the pill mass must be thoroughly kneaded; for small quantities a mortar and pestle may be used. The ingredients are well blended with the operator using as much weight on the pestle as he can exert. The excipient is added as needed to give the proper degree of plasticity. On a large scale, mechanical equipment is used to give the same degree of thorough kneading.

Formerly pill masses represented an official class of preparations under the Latin name of *Massa*. The pill masses were given official recognition because they were kept in bulk by pharmacists for the extemporaneous preparation of pills.

Rolling the Pills

The pill mass is placed on a glass pill tile and rolled into a cylinder or pipe with a smooth flat board. See Fig. 89-47. When the pill pipe has been rolled to the proper length, it is placed over the scale on the pill tile. The place to cut each pill is indicated with a spatula, making only a slight depression in the mass. When the pills have been marked, the pill pipe is cut into the desired number of pills. The pieces of mass are rolled into globular form between the fingers. After the pills have been rolled into the desired form with the fingers, they may be further smoothed using a flat board.

To prevent the pill cylinder from sticking to the tile or board, an absorbent powder is dusted on the surface. This may be rice flour, powdered magnesium carbonate, lycopodium, powdered althaea, powdered glycyrrhiza, or starch.

When pills were a popular dosage form, there were a number of manual pill machines available to make larger quantities of pills more quickly. They were devised to cut the pill pipe

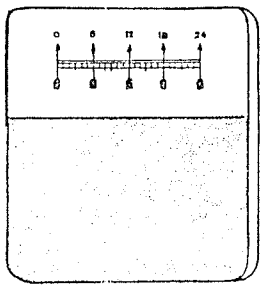


Fig. 89-47. Pill tile.

into equal sections and subsequently to roll the segments into perfectly round pills. Manual pill machines can be seen in many pharmaceutical museums.

Pill-Making Machines

Most pills manufactured today are made on equipment similar to the machines illustrated in Fig. 89-48. The machine on the left makes the mass homogeneous and passes the kneaded mass in the shape of balls to the machine on the right, known as the automata. The automata works the mass into a pill cylinder and divides the piping into pieces of uniform size and weight. By the time the pieces leave the machine they have been rolled into perfect spheres. The automatic pill machine can produce 2-gr pills at the rate of 100,000/hour.

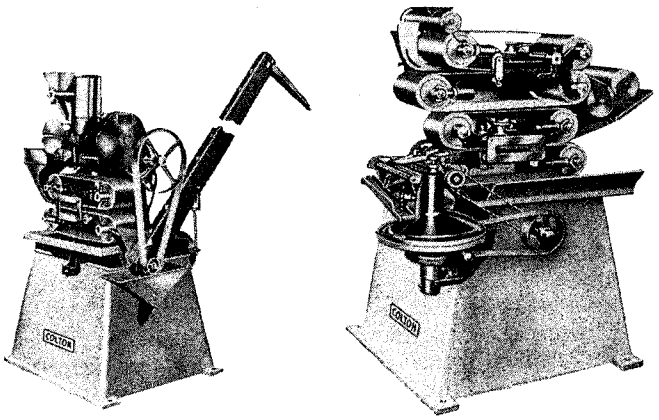


Fig. 89-48. Automatic pill machine (courtesy, Vector/Colton).

Another method for the preparation of pills which has been proposed but not used extensively is the drop method. In Scandinavian countries it has been used for the preparation of vitamin A and D pills. In this method the active ingredients are dissolved or emulsified in material having a suitable congealing point. In the molten or liquefied state they are added as drops to a liquid in which they are insoluble and which has a specific gravity lower than the formed drops. The drops fall slowly through the liquid assuming a round spherical shape due to the surface tension of the melt, and the drops are congealed due to the temperature of the liquid at the end of their passage. Formerly the method was limited to fatty materials but has been applied recently to water-soluble or dispersible materials. Uniform and exact dosage is the chief advantage claimed for the method.

Therapeutic agents are also being compressed in spherical form on tablet machines and when coated, these tablets resemble pills.

Other Solid Dosage Forms

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 holes are to be placed in troches or candy pieces, core-rod tooling is used (see Fig. 89-49). 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.

Cachets

Related to capsules, inasmuch as they provide an edible container for the oral administration of solid drugs, cachets

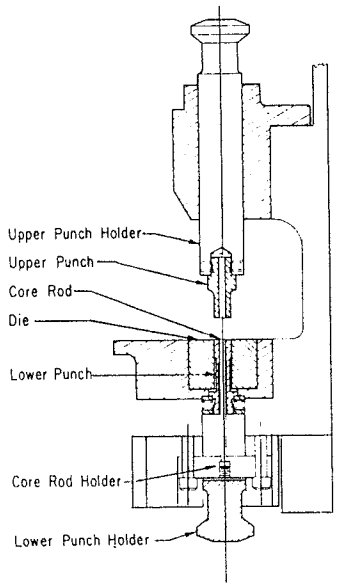


Fig. 89-49. Core rod tooling for compressing troches or candy pieces with hole in center (courtesy, Vector/Colton).

were formerly used in pharmacy. They varied in size from ¾ to ⅛ in. in diameter and consisted of two concave pieces of wafer made of flour and water. After one section was filled with the prescribed quantity of the medicinal agent, they were 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 99

Patient Compliance

consequences of noncompliance
the noncompliant patient
factors associated with noncompliance
patient/health professional interaction factors
improving compliance

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The significant advances that have been made in the understanding of the etiology of many disease states, and the development of new therapeutic agents, have made it possible to cure or provide symptomatic control of many clinical disorders which previously had been difficult to manage. However, concurrent with the increasing sophistication relative to diagnostic and therapeutic knowledge and skills has been a growing recognition that, in many circumstances, drugs are not being used in a manner conducive to optimal benefit and safety. More and more frequently very basic questions regarding drug usage are being asked. Does the patient understand how to take his medication and, if so, is it being taken according to the directions provided? Although problems concerning patient compliance with instructions have been recognized for years, these problems continue to be prevalent and it has only been relatively recently that this issue has begun to receive the attention it deserves.

When the complexity of the patient's illnesses and the actions of potent therapeutic agents are taken into account, the physician and other health professionals can easily become preoccupied with the diagnosis of the disease state as well as the selection and implications of drug therapy and assume that the patient will follow the instructions provided. After all, the medication is being provided to improve and/or maintain the patient's health so why would the patient not cooperate by following instructions? Yet studies continue to show that a large percentage of patients, for a variety of reasons, do not take their medication according to instructions.

Patient Noncompliance

With regard to provision of health care the concept of noncompliance can be broadly viewed, as it relates to instructions concerning diet, exercise, rest, return appointments, etc., in addition to the use of drugs. However, it is in discussions concerning drug therapy that the designation, "patient noncompliance" is most frequently employed. It is in this context that it will be used in this discussion and patient noncompliance can be considered to involve those situations in which the patient does not follow the intended instructions for use of a medication. The expressions, "drug defaulting," "non-adherence," and "non-concordance" have also been employed in discussions of these problems.

The term "patient noncompliance" suggests that the patient is at fault for inappropriate use of medication. Although this is often the case, it has become apparent that responsibility for many cases of noncompliance should more appropriately be directed at the physician and/or pharmacist for failing to give the patient adequate instructions or not presenting them in a manner he understands.

Although the studies reported to date have indicated a wide variation in the degree of noncompliance, in most studies at least a third of the patients failed to comply with instructions and in some studies the rate of noncompliance exceeded 50%. The type of actions most commonly identified as evidence of noncompliance included omission of doses, errors of dosage, errors in the time of administration of the drug, and taking a drug for the wrong purpose. To provide a better insight into the extent of the specific problems identified, the results of several studies are reviewed.

In one study[1] of 134 patients who received 380 prescriptions it was judged that errors of major clinical significance were committed on 118 prescriptions (31% of those studied). The most significant type of error was not having the prescription filled, which occurred in 24 cases. The most common error involved use of the medication at improper dosing intervals, although in most cases these occurrences were not considered to be clinically significant. The most frequently occurring error thought to be clinically significant involved premature discontinuation of the drug by the patient.

Several studies involving use of digoxin present some interesting implications. Of a group of 101 patients evaluated in one study,[2] 66% were judged to be fully compliant on the basis of questioning. The mean serum-digoxin concentrations were determined to be significantly lower in the group of noncompliant patients, leading the investigators to conclude that "patient compliance is a major (if not *the* major) determinant of outpatient serum digoxin concentration." It was also noted that of patients not also taking diuretics 82% were compliant, whereas only 60% of patients taking both digoxin and diuretics were compliant. Another observation of interest in this study was that even noncompliant patients were thought to be under adequate therapeutic control. This seemed to indicate that some patients could be successfully treated with dosages of digoxin that were less than initially prescribed and it was suggested that some patients could perhaps be managed with the use of a diuretic alone.

The therapeutic equivalence and bioavailability of digoxin preparations have received considerable study and publicity in recent years. Although attention to these matters should continue to receive high priority it appears that the factor of noncompliance is much more likely to be responsible for unexpected or altered therapeutic responses.

Another study[3] which showed that 51% of patients in the outpatient setting were noncompliant for written prescriptions prompted an investigation of how patients interpret instructions provided on prescription labels. Sixty-seven patients were asked to interpret instructions on each of ten prescription labels and in not one case was a label uniformly interpreted by all patients. Even when the instructions were not felt by the prescriber to be ambiguous there was frequent misinterpretation with the incidence of interpretive errors ranging from 9 to 64%.

Noncompliance among hypertensive patients is well recognized; in one survey,[4] only 64% of those on medication stated they were taking their medicine all the time as prescribed, while approximately 25% said they never took any.

Problems of compliance have also been frequently noted among elderly patients, many of whom have been prescribed complex therapeutic regimens. In a recent study[5] of 50 in-

dividuals aged 65 years and older who were living independently in the community, it was observed that 66% of the medications were being taken without adequate instructions and 25% of the medications were not being taken as labeled.

Similar problems have been reported in pediatric patients. In a study of compliance[6] with treatment of acute otitis media in 300 pediatric outpatients, complete compliance in taking prescribed antibiotics was only about 7%. Parents gave fewer than the prescribed number of doses in 36% of cases and therapy was discontinued early in 37%. Other factors contributing to the noncompliance included incorrect labeling and the use of "teaspoons" having widely varying volumes.

The likelihood of noncompliance is greatest in outpatients since there is a lesser degree of supervision of the therapy and most studies of these problems have been in this group of patients. However, although understandably not as prevalent, noncompliance can also be a problem in patients who are hospitalized or under similar close supervision. The results of one investigation[7] indicate that one in five inpatients did not take the medications given them by the nursing staff as compared to a 48% incidence of noncompliance among outpatients at the same hospitals. The practice of some patients, in particular patients being treated for psychiatric disorders, to "cheek" their medication until the nurse leaves the room is well recognized.

Consequences of Noncompliance

The consequences of noncompliance, although seemingly apparent, are often not fully appreciated. In many cases noncompliance will result in underutilization of a drug, thereby depriving the patient of the anticipated therapeutic benefits and possibly resulting in a progressive worsening of the condition being treated. Attention has been called to the resulting paradox of undermedicated people living in an overmedicated society.

Several examples of problems can be cited. A patient may discontinue taking an antibiotic for treatment of an infection when the symptoms subside and therefore not use all the prescribed medication. This could result in a recurrence of the infection since the shorter course of therapy was not sufficient to eradicate it. Patients with infections such as tuberculosis have on many occasions been classified as being refractory or developing resistance to agents such as isoniazid when there is a relapse. However, in a number of such cases the relapse has resulted from noncompliance rather than development of resistance to the drugs.

In the management of hypertensive patients, if the physician is unaware that the patient is not taking the medication according to directions and sees that the elevated blood pressure is not well controlled, he may prescribe larger doses of the same agent(s) or prescribe more potent antihypertensive medications. This will expose the patient to a greater risk of adverse effects. Therefore, before a patient is judged to be unresponsive or not optimally controlled with the initial therapy prescribed, it should be ascertained that the medication is being taken according to instructions. True resistance to an antihypertensive regimen is uncommon and it is noted in one commentary[8] that the term "resistant" may more often apply to the patient than the hypertension. Others have noted that malignant hypertension is usually a preventable complication which can be avoided by careful follow-up and seeing that patients take their medication in the appropriate manner.

There has been considerable discussion about the potential risks associated with the abrupt discontinuation of therapy with antihypertensive drugs, in particular clonidine (*Catapres*) and propranolol (*Inderal*). Opinions differ as to the incidence and severity of the problems which could result. However, there have been reports of rebound hypertension when antihypertensive agents have been suddenly withdrawn and additional complications such as worsening of angina and hyperthyroidism may be associated with propranolol withdrawal. Patients should be advised of the risks of missing doses, and when it is desired to discontinue the drug(s), the dosage should be gradually reduced over a period of several days.

A recent report[9] has called attention to hazards of noncompliance with anticonvulsant drug regimens. In examining autopsy records pertaining to 11 cases of unattended, unexpected deaths of epileptic patients, no anticonvulsant drugs were found in four patients and subtherapeutic levels were noted in six others. It is suggested that a number of these deaths may have been preventable had there been better compliance with the instructions for using the medication(s).

The underutilization of one drug may actually result in an excessive response to other agents being employed concurrently. Agents such as digoxin and hydrochlorothiazide (*HydroDiuril*) are frequently used together in patients with congestive heart failure, and potassium chloride is also often administered to replace the potassium that is excreted as a result of the action of the diuretic. If the patient were to stop taking the potassium chloride, potassium depletion could result, making the heart more sensitive to the effect of digoxin. That this type of a problem is a definite possibility is borne out by the results of a study[10] in which the compliance rate for potassium chloride was only 60% as compared to 92% for digoxin and 83% for hydrochlorothiazide. Therefore, noncompliance is a contributing factor to the rather large number of cases of potassium depletion and toxicity of cardiac glycosides that continue to occur with frequency.

Noncompliance may also result in overutilization of a drug. When excessive doses are employed or when the medication is given more frequently than intended there is increased risk of adverse reactions. These problems may develop rather innocently, as in the case where a patient recognizes that he has forgotten a dose of medication and doubles the next dose to make up for it. Some other patients apparently subscribe to a philosophy that if the one-tablet dose that has been prescribed provides some relief of symptoms, two or three tablets will be even more effective.

The problems associated with drug misuse and abuse, whether unintentional or deliberate, are well recognized. Although usually not thought of in terms of noncompliance, drug abuse problems sometimes result from excessive use of medications which have been prescribed for existing clinical disorders.

Another implication of noncompliance relates to the storage of drugs that are not completely utilized in the immediate period after they are dispensed. Keeping these drugs may result in their inappropriate use at some later time. Accidental poisonings have resulted, and stockpiled medications have been used to commit suicide.

It should also be recognized that some individuals use medication that has been prescribed for relatives or friends. Although this practice might not technically be included in the concept of noncompliance, it does reflect an attitude toward use of drugs that can result in problems. In one study[11] of 75 patients it was found that 9 were using drugs that had been prescribed for other individuals.

The recognition that noncompliance is so prevalent has raised questions regarding the attention this variable has received in clinical trials of new therapeutic agents. Although numerous controls are built into these studies, the difficulty in assuring compliance and the potential changes in therapeutic response resulting from noncompliance dictate that close attention be given to this aspect of the study of the action of therapeutic agents.

The Noncompliant Patient

Studies of noncompliance have employed several methods of obtaining data. These include patient interviews, testing for presence of the drug in blood or urine, use of urine markers such as riboflavin or phenol red, and counting the remaining dosage units in the prescription container. Although valuable information has been obtained utilizing these approaches, each method does have limitations.

A distinction has been made between attitudinal and behavioral compliance,[12] since often the attitude and behavior of a patient may be incongruent. For example, a patient may fully intend to take the medication according to instructions but actually not do so because he is forgetful or does not really understand the instructions. On the other hand, some patients may have no intention of complying but nevertheless do so.

Efforts have been made to demonstrate the relationship of noncompliance to a number of variables such as age, education, occupation, socioeconomic status, personality factors, physiologic variables, and the number, types, and severity of illnesses. Although certain patterns have been noted in some studies, the results, in general, have been inconsistent and it continues to be difficult to identify which patients are most likely to be noncompliant.

In several studies in which physicians were asked to predict their patients' compliance, the results were little better than could be obtained by chance. In a recent study,[13] it is reported that the physicians' estimates of patient compliance with an antacid regimen were significantly better than chance but nevertheless low in accuracy. The physicians in the study overestimated their patients' compliance to a regimen by about 50%, and patients overstated their compliance with the regimen by about 100%. Although considerable progress has been made in recognizing and addressing the problems associated with noncompliance, an observation made in an early discussion[14] of this subject continues to be valid today—"It has not proved possible to identify an uncooperative type. Every patient is a potential defaulter; compliance can never be assumed."

Considerable attention has been directed toward the sociobehavioral determinants of compliance and a "health-belief" model which may be helpful in understanding patient behavior concerning matters pertaining to their health. Initially suggested by Rosenstock,[15] the "health-belief" model was originally developed to explain preventive health behaviors such as obtaining immunizations and prophylactic dental care. However, it has also been useful in addressing the problem of noncompliance.

With respect to compliance with treatment regimens, the model consists of the following elements. If compliance is to be achieved, the patient must believe (1) that he actually has the illness which has been diagnosed, (2) that the illness could cause severe consequences with regard to his health and daily functioning, (3) that the treatment prescribed will reduce the present or future severity of the condition, and (4) that the benefits of the regimen prescribed outweigh the perceived disadvantages and costs of following the recommended action. In addition, there must be a stimulus to trigger the advocated health behavior, which can be either internal (e.g., concern about the disease) or external (e.g., interaction with the physician or pharmacist).

Although the "health-belief" model does have certain limitations, it provides a useful basis for studying and predicting patient response to instructions regarding a therapeutic regimen. A number of studies have demonstrated that inappropriate health beliefs are often associated with the occurrence of noncompliance.

There are also other "patient factors" which may result in noncompliance. Patients with chronic illnesses are more likely to be noncompliers as are children and the elderly. Patients who live alone are less likely to comply than those who live with another family member who can take an interest in and/or supervise their therapy.

The increasing problems of drug abuse and addiction have increased the awareness and concern about becoming dependent on agents that are prescribed for legitimate medical reasons. Although drugs that carry a potential for abuse and development of dependence are often prescribed and utilized too casually, some patients develop a fear of dependence regarding use of any drug that is to be employed for a prolonged period. To avoid such a possibility or to prove to themselves that they are not dependent, they may interrupt or stop therapy, or use the medication in smaller amounts.

Numerous other factors have been suggested to contribute to patient noncompliance and the more important of these are considered in the following discussion.

Factors Associated with Noncompliance

In addition to the patient factors previously considered, a number of other determinants of patient compliance have been cited. These have been carefully analyzed by Haynes,[16] who has identified determinants whose association with noncompliance has been confirmed by research studies, and has also discussed other factors which have been suggested, but not conclusively documented, to contribute to noncompliance.

Some of the more important and/or commonly considered factors are discussed below. Although the relationship of some of these factors to the occurrence of noncompliance has not been proven, there should be an awareness of the potential implications in selected patients.

Disease Factors

The nature of the patient's illness may, in some circumstances, contribute to noncompliance. In patients with psychiatric or emotional disorders, the ability to cooperate may be compromised by the illness as well as the attitude toward treatment, and these individuals are more likely than other patients to use medications erratically.

Patients with chronic illnesses, particularly conditions such as hypertension which are often not associated with significant symptomatology, are also more likely to be noncompliers. Patients understandably tend to become discouraged with extended therapeutic programs that do not produce "cures" of the conditions. Even when "cures" can be anticipated as a result of long-term therapy, problems can still occur, as exemplified by patients with tuberculosis who frequently become noncompliant as the treatment period continues. It might be anticipated that when a patient has a life-threatening condition or when significant symptoms of the disease develop if the therapy is prematurely discontinued that the patient will be more attentive to taking medication correctly. For example, a high rate of compliance was noted in a study[17] of patients with cystic fibrosis, suggesting that perception of the severity of the disease and the possible consequences of discontinuing therapy motivated compliance.

Therapeutic Regimen Factors

Multiple Drug Therapy—Although several studies suggest otherwise, it is generally felt that the greater the

number of drugs a patient is taking the higher is the risk of noncompliance. Even when rather specific dosage instructions for the medications are provided, problems can still occur. For example, many geriatric patients are taking five or six or more medications several times a day at different times. It becomes easier to understand how geriatric patients can become confused regarding their therapeutic regimen when one considers how often healthy young women have difficulty in taking oral contraceptives according to a simple dosage schedule using specially designed packages. In addition, some geriatric patients may experience lapses of memory that make noncompliance even more likely. In situations in which multiple drug therapy suggests a significant risk of noncompliance, consideration should be given to discontinuing "nonessential" medications (e.g., multivitamins), if circumstances warrant.

The similarity of appearance (e.g., size, color, shape) of certain drugs may contribute to the confusion that can exist in the use of multiple drugs. It is desirable that there be an awareness of the physical characteristics of the drugs utilized so that the patient will not be taking, for example, only small white tablets. In one report,[18] serious complications experienced by two patients are described, which were apparently attributable to the patients' confusing digoxin, 0.25 mg, with furosemide (*Lasix*), 40 mg, another small white tablet.

Although combination drug products have a number of disadvantages and have received quite a bit of negative publicity in recent years, their use may help improve compliance with therapy since only one tablet need be administered rather than several. The issue of compliance provides a reasonable argument for the use of combination products although some have raised questions as to whether the available evidence supports claims of improved compliance. Therapy should not be initiated with a combination product but rather with the individual agents. Once the optimal dosages of the individual drugs have been determined, if they correspond to the amounts included in the combination, these products can be used to advantage.

Frequency of Administration—Just as use of multiple drugs contributes to noncompliance so does use of an individual drug at frequent intervals. This situation makes it more likely that the patient's normal routine or work schedule will have to be interrupted to take a dose of medication and in many cases the patient will forget, not want to be inconvenienced, or even be embarrassed to do so.

Many drugs must be given at frequent intervals to maintain desired blood and tissue levels. However, some drugs that have traditionally been administered three or four times daily have been found to produce just as good a response when administered once daily. For many years isoniazid was administered in a dosage of 100 mg three times daily. However, it has been shown that the use of a 300-mg dose once daily produces equally effective results and some investigators are studying its use at even less frequent intervals. Studies also indicate that some antihypertensive agents, the antipsychotic agents, and tricyclic antidepressants can also be administered less frequently, often on a once-a-day basis. In an investigation[20] that evaluated the frequency of administration of a single drug on compliance over a one-month period, the following results were obtained: four times daily—70% failed to take 25 to 50% of the prescribed dose; three times daily after meals—60% failed to take 25 to 50% of the prescribed dose; twice daily—30% failed to take up to 25% of the prescribed dose; and once daily—7% failed to take up to 20% of the prescribed dose. In this study it was observed that patients who took nonprescription medications such as vitamins, aspirin, and laxatives, rarely failed to do so daily. Taking their nonprescription drugs had become a part of their regular routine or habit, and it is recommended that use of prescription drugs be incorporated into some part of the patient's daily routine in an effort to improve compliance.

Use of drugs at less frequent intervals will only be successful with certain drugs, particularly those that have long half-lives and have a sufficient interval between the blood levels that produce a therapeutic response and those that can result in the development of adverse effects. If the latter situation was not the case, the use of larger doses at less frequent intervals could provide blood levels that result in adverse effects.

Duration of Therapy—Several studies have shown that the rate of noncompliance becomes greater when the treatment period is long. As noted earlier, a greater risk of noncompliance should be anticipated in patients having chronic disorders, especially if discontinuation of therapy is not likely to be associated with prompt recurrence of symptoms or worsening of the illness.

Adverse Effects—Development of unpleasant effects of a drug is a likely deterrent to compliance although several studies suggest that this is not as important a factor as might be expected. In some situations it may be possible to change the dosage or use alternative drugs to minimize adverse effects. However, in other cases these alternatives may not exist and the benefits expected from therapy must be weighed against the risks. Particularly disconcerting are those situations in which the development of side effects makes the patient feel worse than he did before therapy was initiated, as often occurs in hypertensive patients.

It has been noted that development of impotence is a major reason for male patients to discontinue taking antipsychotic medications; this observation also relates to use of certain other drugs.

Even a warning about possible adverse reactions may result in some individuals not complying with instructions. It is inadvisable for patients being treated with sedatives or tranquilizers to consume alcoholic beverages because of the possibility of an excessive depressant effect. However, there should be a realistic recognition that many patients, if faced with a mandate not to drink while on drug therapy, will choose not to take their prescribed medication. Although problems of combined alcohol-drug usage are well known, this situation continues to present a challenge of effectively communicating with the patient so that optimal benefit can be achieved at minimal risk. Every patient for whom a depressant drug has been prescribed should be alerted to the fact that this effect may be enhanced by alcohol. If it is anticipated that the patient will not cooperate in completely avoiding alcoholic beverages, he should be urged to use them in moderation, particularly when therapy is initiated, and cautioned to observe his own tolerance when they are employed in combination. However, the fact that many individuals can take depressant drugs and consume relatively large amounts of alcoholic beverages with no apparent difficulty should not be cause to forget that such combinations have proven lethal in some individuals.

Patients May be Asymptomatic or Symptoms Subside—It is understandably difficult to convince a patient of the value of drug therapy when the patient has not experienced symptoms prior to initiation of therapy. Such is often the case in the treatment of hypertension, and the lack of previous symptoms coupled with the probable lack of appearance of symptoms if therapy is discontinued contributes to the high rate of noncompliance in these patients.

Other situations in which the benefits of drug therapy are not directly apparent include circumstances in which a drug is used on a prophylactic basis. Noncompliance is often seen in children for whom penicillin has been prescribed prophylactically to prevent recurrence of rheumatic fever. Since the cooperation of the mother in giving penicillin to the child is often difficult to achieve, many physicians prefer to give monthly injections of benzathine penicillin G (*Bicillin*).

In other circumstances the patient may feel better after taking the drug and feel that he no longer needs to take it once the symptoms subside. Situations frequently occur where a patient does not complete a full course of antibiotic therapy once he feels that the infection has been controlled. This practice increases the likelihood of a relapse of the infection.

Cost of Medication—Although noncompliance does frequently exist with the use of drugs that are relatively inexpensive, it might be anticipated that patients will be even more reluctant to comply with instructions for the use of more expensive agents.

The expense involved has been cited by some patients as the reason for not having prescriptions filled at all, whereas in other cases the medication is taken less frequently than intended or prematurely discontinued because of the cost. Antibiotics are among the higher priced drugs, and it is recognized that some patients will discontinue taking the drug as soon as symptoms subside so that they can save the balance of the medication for similar problems they may encounter in the future.

One observer has noted[21] that psychiatrists often prescribe expensive medication that some patients cannot afford. He goes on to state that "many people would rather be sick than poor or at least they would be willing to be less than healthy if they could remain relatively wealthy—something doctors seldom understand."

Measurement of Medication—Although a patient may fully intend to comply with instructions, he may inadvertently receive the wrong quantity of medication due to incorrect measurement of medication or use of inappropriate measuring devices. In one study[6] of the use of antibiotics in pediatric patients, the volume of 130 "teaspoons" was measured and found to vary from 2 to 9 ml. The inaccuracy of using teaspoons to administer liquid medications is compounded by the possibility of spillage and when the patient is called on to measure a fraction of a teaspoonful. Although this problem has been long recognized, it has still not been effectively addressed and the importance of providing the patient with measuring cups, oral syringes, or calibrated droppers for the use of oral liquids is evident.

Another situation in which measurement of medication has presented problems is seen with use of insulin. The confusion or misunderstanding that has resulted in administration of incorrect doses of insulin is well recognized, although the use of the U-100 insulins has significantly reduced these problems.

Unpleasant Taste of Medication—Taste problems of medications are most commonly encountered with the use of oral liquids by children. Getting a child to take a dose of medication may be such a difficult task for a parent that noncompliance may result or administration of the drug discontinued as soon as the parent sees any sign of improvement. However, compliance problems relating to the taste of medication are not limited to children. Objections to the taste of liquid potassium chloride preparations are often raised; a number of patients discontinue taking the medication for this reason. This is borne out, in part, by a study[10] cited earlier in which it was noted that compliance in taking potassium chloride was less than with digoxin or hydrochlorothiazide. For patients who object to the taste of the available liquid potassium chloride preparations, the use of sustained-release potassium chloride tablets (*Slow-K*) might be considered.

Patient/ Health Professional Interaction Factors

The circumstances surrounding the visit of a patient with a physician and/or pharmacist, and the quality and effectiveness of the interaction and communication of these health professionals with the patient, are major determinants of the patient's understanding of and attitude toward his or her illness and therapeutic regimen. One of the patient's greatest needs is psychological support provided in a compassionate manner and it has been observed that patients are more inclined to comply with the instructions of a physician they know well and respect, and from whom they receive information and assurance about their illnesses and medications.

One group of investigators[22] has viewed the patient-physician interaction as a negotiation among two active and equal participants with a strategy which includes the elements of "putting the ill at ease," respect, positive attitude, information, translation, feedback, patient response, and negotiation. Respect for the patient and a realistic appraisal of the circumstances of the individual patient are essential if therapeutic goals are to be achieved. One observer[23] has called attention to the difference between rational prescribing on a clinical pharmacological basis and realistic prescribing for the individual patient. The former approach represents a narrow concept which regards the patient as an object of therapeutic decisions, whereas the latter recognizes the patient as an individual with personal characteristics who must cooperate and share in the responsibilities pertaining to his therapy.

In advocating "participant prescribing," another clinician takes note[24] of the observations[25] of a layman in commenting on the physician-patient relationship—"I will tear up my doctor's prescriptions when I doubt that he has heard me. Why should I take his word, when he is not even paying me the courtesy of listening to mine."

The following factors are among those which could adversely influence compliance if there is inadequate attention to the considerations discussed above.

Waiting to See the Physician or Pharmacist—When a patient experiences a significant wait in getting to see his physician or having his prescription filled, the annoyance may contribute to poorer compliance with the instructions provided. In one study[26] it was noted that only 31% of the patients who usually wait more than 60 minutes to see their physicians are full compliers as opposed to 67% of the patients who see the physician within 30 minutes of the time they arrive. In another investigation[27] designed to determine why about one-half of the patients had dropped out of a hypertension clinic, it was noted that about two-thirds of the patients complained about the time it took to see the physician, with the average waiting time being 2½ hours. In addition, the patients waited an average of 1¾ hours to obtain their prescriptions at the pharmacy. By comparison, the actual time spent with the physician and pharmacist was almost negligible. Efforts to reduce these delays have resulted in a more favorable patient response and a lower dropout rate.

Failure to Comprehend the Importance of Therapy—A major reason for noncompliance is that the importance of the drug therapy and the potential consequences if the medication is not used according to instructions have not been impressed upon the patient. Patients usually know relatively little about their illnesses, let alone the therapeutic benefits and problems that could result from drug therapy. Therefore, they establish their own ideas regarding their conditions and their own expectations of the effect of drug therapy. If the therapy does not then meet these expectations they are more inclined to become noncompliant. Greater attention to educating the patient regarding his condition as well as the benefits and

limitations of drug therapy will contribute to a more cooperative attitude on the part of the patient.

Poor Understanding of the Instructions—Numerous investigations have described problems of this type. In one study[28] of approximately 6000 prescriptions, 4% were written with the designation for patient instructions being "as directed." In following up on 151 of these prescriptions it was found that in 36 cases the patients had received auxiliary written instructions from the prescriber. Of the other 115 prescriptions the patient gave the same instructions that the physician intended (as determined by contacting the physician) in 71 cases but in 44 cases the understanding of the directions on the part of the patient was different than that intended by the prescriber. The possible consequences of some of these misunderstandings could be serious. For example, one patient was going to take two phenytoin capsules (100 mg) three times daily rather than one capsule three times daily as the physician intended. Another patient would have used oral contraceptive tablets incorrectly, and it is of interest to note that the patient had become pregnant once before while taking oral contraceptives. In another case the patient was planning to use 45 units of insulin each day, whereas the physician intended that she only use 27 units each day.

Even when directions to the patients are more specific than "as directed," confusion can still occur. In a study[3] of interpretation of prescription instructions it was shown that there were frequent errors of interpretation even when the instructions were not thought by the prescriber to be ambiguous. For example, in interpreting a prescription that read "Tetracycline, 250 mg every six hours," only 36% of the 67 patients in the study indicated they would take the drug every six hours around the clock for a total of four doses each day. About 25% of the patients would not take a night-time dose since they divided the time that they were awake into three six-hour periods. A prescription for penicillin G was written to be taken "three times a day and at bedtime," and about 90% of the patients indicated that they would take the drug with meals and at bedtime. Taking the drug in this manner could result in a significant decrease in its absorption.

Some drugs, such as nitrofurantoin (*Furadantin, Macrodantin*) and indomethacin (*Indocin*) are best taken on a full stomach to minimize gastrointestinal irritation. When the term "with meals" was employed in the patient directions, about half of the patients would have taken the drug before meals, sometimes as long as an hour before. It was found that there was an improved interpretation of the instructions when they were written "to be taken immediately after food four times a day," although interpretive errors were still not completely eliminated.

A prescription for chlorpropamide (*Diabinese*) was written with instructions to take the drug "every twelve hours" but 36% of the patients would not have taken the drug at this interval. A particularly interesting response was seen with a prescription designated "Furosemide, 40 mg as needed for fluid retention." The patients were asked whether the medication allowed one to keep the fluid inside the body or helped to eliminate fluid from the body and more than half the patients felt that the drug would cause one to retain fluid. In this case the confusion involved the use of the word "for," as many interpreted it as *causing* the circumstances designated rather than *preventing* or *correcting* them.

The designation "as needed" in the instructions is also subject to varying interpretations.[29] Patients shown a label for a prescription for propoxyphene (*Darvon*) with the directions "every 4 hours as needed," were asked to indicate the maximum number of capsules permitted in 24 hours. Approximately one-half responded incorrectly, with the responses ranging from two to eight capsules.

In another study[30] of 451 outpatient prescriptions it was found that in 70 cases the patients were unable to interpret a dosage schedule from the instructions provided or only had a vague idea of how to use the drug. In 161 cases the instructions were to administer the medication two, three, or four times daily (bid, tid, or qid). When the patients were asked the specific times they would take the medication the responses varied greatly. The following are cited as examples of individual problems. One patient who was to take two doses of sulfamethoxazole (*Gantanol*) a day scheduled the doses within four hours of each other. Another patient would have taken four tetracycline doses per day at two-hour intervals, and yet another patient would have taken four doses of methenamine mandelate (*Mandelamine*) at one-hour intervals in the morning.

These studies point out the confusion that may exist on the part of the patient even when instructions are seemingly clear. However, many prescriptions are written and labeled to indicate how many doses are to be taken each day with no additional clarification as to how the doses are to be scheduled. For example, how should instructions to take one tablet three times daily be interpreted: Does this mean every eight hours, or with meals, or possibly some other schedule? If the drug is to be given with meals or at a specified time before or after meals, it is usually assumed that the patient eats three meals a day. Yet this is not always the case. Some drugs that are given several times a day include a bedtime dose. However, there can be a wide variation among patients in the time that this dose would be administered.

Nothing should be taken for granted regarding the patient's understanding of how to use medication. Not only are there reports of medications being used according to wrong dosage schedules, but in some cases the uncertainty or confusion on the part of the patient is such that medications are given by the wrong route of administration (e.g., instilling oral pediatric antibiotic drops into the ear for an ear infection). In one study[31] it was observed that a number of patients would frequently request their physicians to write new prescription orders. In looking into this situation further it was found that the patients did not know the meaning of the word "renewal" and although the number of renewals was noted on the label the patients did not know that they were able to obtain more medication.

Although not a complete listing of all factors that result in noncompliance, those discussed give an indication of the difficult challenge of assuring optimal drug therapy. Inherent in many of the factors considered is the matter of communication of the physician and pharmacist with the patient. This communication is in many cases not only incomplete and ineffective but often there is the impression that physicians and pharmacists are too busy or not interested in talking with the patient. Improving communications must be considered the key to increasing compliance and some of the approaches and recommendations directed toward this goal are reviewed in the following discussion.

Improving Compliance

In most situations both the physician and the pharmacist have the opportunity to talk directly with the patient about the drugs that have been prescribed; the effectiveness of this communication will be a major determinant of patient compliance. Not to be overlooked is the desirability of also having effective communication between the physician and the pharmacist so that their efforts in the patient's behalf are consistent and harmonious.

Although the physician's role in minimizing noncompliance should not be underestimated, the pharmacist has a particularly valuable opportunity to encourage compliance since his advice accompanies the actual dispensing of the medication and he is the last health professional to see the patient prior to the time the medication is to be used. In addition, the pharmacist may find it easier than the physician to establish rapport with the patient, and this is reflected by the many occasions in which a patient asks a pharmacist about his or her illness or medications because of reluctance to discuss these matters with the physician. In the following discussion particular emphasis is placed on the pharmacist's role in addressing the problem of noncompliance.

Identification of Risk Factors

All patients should be viewed as potential noncompliers. However, a first step in efforts to improve compliance should be to recognize individuals who are most likely to be noncompliant, as judged by a consideration of the risk factors noted earlier. These factors should be taken into account in planning the patient's therapy so that the simplest regimen which is, to the extent possible, compatible with the patient's normal activities can be developed.

Development of Treatment Plan

Although developing the treatment plan has traditionally been the responsibility of physicians, pharmacists have become increasingly involved in this aspect of patient-care. When prescriptions are written, the instructions should be as specific as possible. Instructions such as "as directed" or other directions that are subject to misinterpretation should be avoided. Even such seemingly specific instructions as "one tablet three times daily" are often misinterpreted, as discussed previously. Where possible, and with a recognition of the patient's normal routine, the specific times of day at which the patient is to take the medication should be indicated. In all cases the pharmacist should ascertain that the patient understands how to use the medication.

The American Pharmaceutical Association and the American Society of Internal Medicine have developed a statement on prescription writing and prescription labeling (Appendix A). Not only do the guidelines provide important information and suggestions but the statement reflects the type of interdisciplinary cooperation which must also be achieved in practice if patient needs are to be best served.

So that one important aspect of noncompliance is not overlooked it should be noted that many prescriptions that patients receive from their physicians are never filled. In one study[32] involving 2000 prescriptions, 3% were not filled within 10 days and, in a recent investigation,[33] the rate of noncompliance in initially having the prescription filled was found to be 6%. Relatively little progress has been made in detecting and correcting these occurrences, further emphasizing the need for more effective communication and a closer working relationship between physicians and pharmacists.

It has been noted[34] that the prescription can be used as the organizing instrument of instruction; however, "most often the prescription slip is simply handed over as the closing act of the encounter, while the patient or parent is outward bound." The prescription should signal the start of an alliance, and it behooves the physician to appropriately emphasize its importance.

Evaluating Information

Decisions must be made as to what information should be provided to patients with regard to their disease states and drug therapy. There is considerable information available with respect to any drug that a patient may be taking. Although there is some information which should be provided to a patient, there is other information of which the pharmacist should be aware but which should not be provided to the patient for fear of alarming him.

The importance of exercising careful judgment in making decisions as to the information that should be provided to the patient cannot be too strongly emphasized. This issue has been the basis of considerable controversy regarding the development of patient package inserts as a number feel that the provision of information that is very comprehensive and highly specific relative to the occurrence of adverse effects, etc., may actually discourage the patient from taking his medication. However comprehensive the patient package inserts may be, it must be recognized that they are a supplement to, and do not take the place of, the consultation of the physician and the pharmacist with the patient.

Patient Education

In discussing an illness or drug therapy with a patient a distinction should be made between "information" and "education." Patients may receive information but not understand it and utilize it correctly, whereas education implies understanding and behavioral change. Patients should be encouraged to participate in the discussion and where possible they should be brought in on the decision-making process. They should also be encouraged to ask questions, and it is desirable for the pharmacist, after he has explained the directions for using a drug, to ask the patient if he has any questions as to how the drug is to be used.

To provide the degree of understanding which will lead to favorable therapeutic outcomes, patients should be knowledgeable concerning a number of aspects of their drug therapy. These factors are identified in the "Statement of Pharmacist-Conducted Patient Counseling" developed by the American Society of Hospital Pharmacists (Appendix B). In certain cases some of the factors identified may not be applicable. However, presently, many patients are receiving minimal information and greater attention must be directed to the provision of all the pertinent information to the patient.

The goal of communications with the patient is to provide information that the patient is able to understand and utilize. The approach should be one that will be reassuring to the patient and will not unnecessarily cause alarm, as may be expected when an over-zealous discussion of adverse effects makes the patient afraid to use the drug. Thus, the provision of too much information, or an inappropriate approach in presenting it, can actually contribute to noncompliance rather than prevent it.

Verbal Communication—Communication between the pharmacist and patient regarding the use of medication can be both verbal and written. Although it may be supplemented and reinforced by written instructions, verbal communication is a very important aspect of patient education since it directly involves both the patient and the pharmacist in a two-way exchange and provides the opportunity for the patient to raise questions. For such communication to be most effective it should be conducted in a setting that provides privacy and is free of distractions. The results of several studies[35] have shown greater compliance among patients with whom the pharmacist discussed the therapy in a private consultation room.

Although most pharmacies do not presently have a separate patient consultation area, this is a desirable goal. Not only will this emphasize to the patient the importance the pharmacist attaches to the information being discussed, but it will also further strengthen the recognition of the pharmacist as one who is contributing to the patient's health care. Even in

THE NEW YORK HOSPITAL

PATIENT MEDICATION INSTRUCTION CARD

Dear Patient:

Your physician has prescribed digoxin (Lanoxin®). Digoxin is used to make your heart beat more strongly (and in some cases to control rhythm disturbances or the heart rate). To insure successful treatment of your condition it is essential to follow these instructions:

1. Digoxin should be taken as directed. Avoid missing doses.
2. Never increase, decrease, or change your dose without specific instructions from your physician.
3. Maintain the diet that your physician has recommended.
4. Inform any physician whom you visit that you are taking digoxin.
5. Purchase your digoxin at the same pharmacy whenever possible.
6. If you are also taking a diuretic medication ("water pill"), it is particularly important that you take any potassium supplements that may have been prescribed. Loss of potassium from the body (which may occur with some diuretics) increases certain side effects of digoxin that might be harmful. Potassium supplements, therefore are important for the same action of digoxin and should be taken as prescribed.

Report these signs to your physician if

1. Reappearance of symptoms.
2. Extremely rapid heart rate, or a pulse rate of less than 60 beats per minute.
3. Prolonged loss of appetite, vomiting or diarrhea.
4. Unusually frequent headaches, excessive fatigue, difficulty in falling asleep or confusion.
5. Changes in vision such as green or yellow vision, colored halos or spots around objects, blurred vision or double vision.
6. Skin rash or hives.
7. Rapid weight gain.
8. Increased shortness of breath.

Additional information: _____

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_____

Fig. 99-1. Patient medication instruction card (The New York Hospital, modified).

the absence of such a separate area, however, there must be an awareness of the need for a setting that is conducive to effective communication.

Medication is often obtained in a manner that does not lend itself to verbal communication. For example, the pharmacist may receive a telephoned prescription from a physician that is to be delivered to the patient's home or picked up at the pharmacy by a relative or friend. In these circumstances, when appropriate, the pharmacist might call the patient to discuss the use of the medication.

Written Communication—The emphasis on verbal communication should not be interpreted to indicate that written communication is not important. Although at the time of the visit to the physician or pharmacist the patient may understand how the medication is to be used, he may not later remember the details relating to administration of the drug. Therefore, specific instructions for use should be placed on the prescription label. The importance of accurately designating the intended instructions on the prescription label is obvious. In one study[36] of prescription labeling, however, it was found that the directions for use were grossly incorrect on 2.6% of the labels, with some of the errors attributable to the pharmacist and others to the physician. Additional labels were deficient in other respects. It would seem that some pharmacists do not place enough emphasis on the accuracy, completeness, and neatness of the label. If this is evident to the patient it could reduce their respect for the therapy as well as the pharmacist.

Several approaches have been taken to modify the prescription label in such a manner to call greater attention to the times at which the medication is to be administered. In one study[37] compliance was improved by using labels on which a clock face was imprinted and on which the pharmacist circled the times at which the drug was to be administered. However, in another investigation[29] it is noted that one group of patients who understood the verbal instructions were confused by the clock. It is often desirable to provide supplementary written instructions or other information pertaining to the patient's illness or drug therapy, and many pharmacists are now giving patients medication instruction cards or inserts such as the example[38] shown in Fig. 99-1. In the development of patient education materials it must be recognized that many individuals have a low reading level (and some are functionally illiterate). The approach and content of these materials should reflect this situation.

As excellent as the labeling and supplemental written instructions may be, however, they must still be viewed as one-way communication unless provision is also made to permit the patient to discuss and ask questions about his therapy. Therefore, verbal and written communication should be used to complement each other and both should be viewed as important components of the effort to educate the patient regarding his drug therapy.

Audiovisual Materials—The use of audiovisual aids may be particularly valuable in certain situations since the patient may be better able to visualize the nature of his illness, or how his medication acts or is to be administered (e.g., the administration of insulin). An increasing number of pharmacists have made good use of such aids by making them available for viewing in a patient waiting area or consultation room while

the prescription is being prepared, and then answering questions the patient may have.

Controlled Therapy—It has been proposed[39] that hospitalized patients be given the responsibility for self-medication prior to discharge. Presently, patients go from a complete dependence on others for the administration of their medication while hospitalized to a situation where they are given the full responsibility when discharged, with the assumption often made that the patient knows about his drugs because he was taking them in the hospital. Similar situations are encountered by many ambulatory patients who are expected to be responsible for their treatment, yet have not been provided with adequate information and encouragement.

The suggested arrangement would permit the patient to start using the medication on his own in a setting in which health professionals are available to answer questions and identify problems. It may also be possible at this early stage in the patient's therapy to identify situations that could eventually result in noncompliance.

It has been assumed by many that patients who are knowledgeable about their illness and therapeutic regimen are more likely to be compliant. Although this premise may be valid for many individual patients, several studies suggest that increased patient knowledge does not necessarily alter patient behavior and compliance. In one of these studies,[40] it was noted that some of the most flagrant noncompliers could identify their drugs by name and correctly recite the instructions for use.

The fact that such observations have been made must not detract from patient education efforts and, indeed, there must be a commitment to further enhance these programs. However, there must be an awareness of the need to motivate the patient to use the knowledge that has been acquired for the purpose of achieving optimum benefit from his therapy.

Compliance Aids

Drug Reminder Charts and Devices—Various forms, of which a patient calendar sheet described by Liberman[41] is an example, have been developed and are designed to assist the patient in self-administration of drugs. In addition to their use in helping the patient understand which medication to take and when to take it, the forms, on which the patient is to check the appropriate area for each dose of medication he takes, can be evaluated by the pharmacist or physician when the patient returns for more medication or has his next appointment.

Devices such as MEDISET are also available to help patients organize their drugs and to monitor self-administration of medication on a daily and weekly basis. The device contains 28 compartments, representing four compartments for different time periods (i.e., 7–9 A.M., 11 A.M.–1 P.M., 4–6 P.M., 8–10 P.M.) for each day of the week.

Packaging—The manner in which medication is packaged may also have an influence on patient compliance. Specially designed packaging for oral contraceptives has been valuable in increasing patient understanding of how these agents are to be taken. Special packages of certain steroids to be used for a treatment period of six days (*Medrol Dosepak, Aristo-Pak*) or in an alternate-day regimen (*Medrol ADT Pak*) have been designed to facilitate use of steroids in dosage regimens that may be difficult to understand or remember. Other agents, such as certain diuretics and antibiotics are now also marketed in "compliance packages." In a study of the effect of packaging and instruction on outpatient compliance, Linkewich *et al.*[42] found that special packaging of penicillin V potassium tablets complemented the pharmacist's instructions to the patient in achieving increased compliance.

A possible negative effect of drug packaging on patient compliance is seen with the use of the child-resistant containers. Some patients, particularly the elderly and those with conditions like arthritis and parkinsonism, have difficulty in opening some of these containers and may not persist in their efforts to do so. Pharmacists should be alert to problems of this type and, where appropriate, suggest use of standard containers.

Dosage Forms—New dosage forms of certain drugs have also been developed in large part as a recognition of problems of noncompliance. The increasing practice of using tricyclic antidepressants in larger single evening doses to increase compliance and minimize certain adverse effects has led to the introduction of higher potency formulations such as *Tofranil-PM*.

Another new dosage form has resulted from the recognition that many patients with venereal diseases are not compliant with an antibiotic regimen to be given over a seven to ten-day period, with the result being numerous relapses. Efforts were directed to the use of large single doses of antibiotics and the product *Polycillin-PRB*, containing 3.5 grams of ampicillin and 1 gram of probenecid, has been used as a single-dose treatment for gonorrhea.

Monitoring Therapy

The pharmacist's role in minimizing noncompliance does not end when the prescription is dispensed. If he becomes aware that the patient is not using the drug as intended, he should endeavor to determine the reason and resolve any problem that may exist. The pharmacist is in an excellent position to detect noncompliance pertaining to the use of drugs used in the management of chronic conditions such as hypertension and diabetes by paying close attention to the frequency with which a patient has his prescription renewed. For example, if a 30-day supply of medication has been dispensed to a patient and he does not return for a renewal until 45 days later it may be that the medication is not being taken according to directions. The physician may have told the patient to take the medication less frequently, but more probably the patient did not understand or decided not to follow the instructions; thus the pharmacist should be alert to situations in which the renewal frequency is not consistent with the directions for use.

It is highly desirable that pharmacists utilize systems by which the renewal frequency for chronic medications may be quickly checked so that potential problems can be identified early. If there is one tool that is essential in addressing the challenge of noncompliance as well as other drug-related problems, it is the patient medication record. It is not enough to just maintain these records—they must be used to identify potential problems and to enhance consultation with patients.

A "tickler" file system has been employed successfully in minimizing noncompliance. The tickler is a clip-on attachment which can be affixed to the top of the patient medication record. Self-adhesive colored dots indicate the month the patient should return and a number written on the dot indicates the day of the month.

Once the tickler system is set up, the medication records can be monitored on a daily, or once-a-week, basis. When the pharmacist identifies that a patient has not had his medication renewed by the time that his supply should have been exhausted, he can contact the patient regarding it. It may be found that there is a valid reason for the patient not renewing the prescription at the expected time. Nevertheless, the awareness of the patient that the pharmacist is paying attention to his therapy and has taken a personal interest in contacting him should not only contribute to compliance but also increase the respect of the patient for the pharmacist.

Situations in which drug usage would seem to be excessive, as evidenced by the patient desiring to renew his prescription

more frequently than the directions suggest, represent equally important problems that are easier to detect. Again the pharmacist should attempt to identify the reason for the inconsistency and any problem that may exist.

Conclusion

Considerable time, energy, and expense have often gone into the diagnosis of a patient's illnesses and the development of his treatment program. Yet the goals of therapy will not be reached unless the patient understands and follows the instructions for use of the drugs prescribed. One cannot also help but wonder how often patients have been categorized as treatment failures and have had their therapy changed, possibly to more potent and toxic agents, when the reason for the lack of response or an unanticipated altered response has been noncompliance.

Despite the increasing attention directed to the matter of noncompliance, the problem is still not accorded the attention it deserves and continues to be prevalent. Although the approaches taken and suggestions advanced in an effort to decrease noncompliance have met with varying success, they have significantly contributed to recognition of the problem and provided a valuable base on which to develop modified or new approaches to the problem. Certain approaches that involve a significantly increased commitment of time on the part of physicians and pharmacists may be viewed by some as impractical. Yet can this compare with the commitment of time and expense that is presently wasted as a result of noncompliance?

The pharmacist is the logical health professional to assume major responsibility in minimizing noncompliance. Of priority importance is the need to strengthen communications with patients and physicians. Yet many pharmacists are reluctant to accept, and sometimes even resist, opportunities to become more involved in advising patients or contributing to decisions regarding drug therapy because they do not feel adequately prepared. The desirability of pharmacists increasing their knowledge about disease states and the properties of drugs cannot be too strongly emphasized. However, there is no reason why every pharmacist cannot have at least some initial involvement in decreasing the problem of noncompliance even if it is limited to reviewing the directions with the patient or determining the frequency of renewal of chronic medications. The satisfaction that this contribution to patient-care can bring will serve as a challenge to further increase one's knowledge and professional involvement.

The problem of noncompliance has been identified and is receiving increasing attention. Patients for too long have been deprived of a close attention to and monitoring of their drug therapy. An excuse that pharmacists are too busy to advise patients regarding their drug therapy cannot be accepted; the highest priority must be assigned to taking the steps to ensure that patients will use their medications in the appropriate manner. If pharmacists do not assume the responsibility for decreasing noncompliance, someone else will. The profession cannot afford to default on this valuable opportunity to enhance its contribution to patient care.

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Appendix A—Statement on Prescription Writing and Prescription Labeling*

Introduction

Historically, the pharmaceutical and medical professions have devoted considerable time and effort to the development and rational utilization of safe and effective drugs for the treatment and prevention of illness. Today, that successful effort continues, helping to achieve the highest standards of health in the world for the American people. But in order to gain maximum benefit from the use of drugs while minimizing their adverse side effects, prescribers and pharmacists must maintain effective communications not only among themselves, but with their patients as well. The directions for drug use and other information which prescribers indicate on prescription orders and which pharmacists transfer to prescription labels are critical to safe and effective drug therapy. In order to assure that this information is conveyed clearly and effectively to patients, the following guidelines have been developed by the American Pharmaceutical Association and the American Society of Internal Medicine.

Guidelines for Prescribers

The following guidelines are recommended for prescribers when writing directions for drug use on their prescription orders.

1. The name and strength of the drug dispensed will be recorded on the prescription label by the pharmacist unless otherwise directed by the prescriber.
2. Whenever possible, specific times of the day for drug administration should be indicated. (For example, *Take one capsule at 8:00 a.m., 12:00 noon, and 8:00 p.m.* is preferable to *Take one capsule three times daily.* Likewise, *Take one tablet two hours after meals* is preferable to *Take one tablet after meals.*)
3. The use of potentially confusing abbreviations, i.e., *qid, qod, qd,* etc., is discouraged.
4. Vague instructions such as *Take as necessary* or *Take as directed* which are confusing to the patient are to be avoided.
5. If dosing at specific intervals around-the-clock is therapeutically important, this should specifically be stated on the prescription by indicating appropriate times for drug administration.
6. The symptom, indication, or the intended effect for which the drug is being used should be included in the instructions whenever possible. (For example, *Take one tablet at 8:00 a.m. and 8:00 p.m. for high blood pressure,* or *Take one teaspoonful at 8:00 a.m., 11:00 a.m., 3:00 p.m., and 6:00 p.m. for cough.*)
7. The Metric System of weights and measures should be used.
8. The prescription order should indicate whether or not the prescription should be renewed and, if so, the number of times and the period of time such renewal is authorized. Statements such as *Refill prn* or *Refill ad lib* are discouraged.
9. Either single or multi-drug prescription forms may be used when appropriately designed, and pursuant to the desires of local medical and pharmaceutical societies.
10. When institutional prescription blanks are used, the prescriber should print his/her name, telephone number, and registration number on the prescription blank.

Guidelines for Pharmacists

1. Pharmacists should include the following information on the prescription label: name, address, and telephone number of pharmacy; name of prescriber; name, strength, and quantity of drug dispensed (unless otherwise directed by the prescriber); directions for use; prescription number; date on which prescription is dispensed; full name of patient; and any other information required by law.
2. Instructions to the patient regarding directions for use of medication should be concise and precise, but readily understandable to the patient. Where the pharmacist feels that the prescription order does not meet these criteria, he should attempt to clarify the order with the prescriber in order to prevent confusion. Verbal reinforcement and/or clarification of instructions should be given to the patient by the pharmacist when appropriate.
3. For those dosage forms where confusion may develop as to how the medication is to be administered (for example, oral drops which may be mistakenly instilled in the ear or suppositories which may be mistakenly administered orally), the pharmacist should clearly indicate the intended route of administration on the prescription label.
4. The pharmacist should include an expiration date on the prescription label when appropriate.
5. Where special storage conditions are required, the pharmacist should indicate appropriate instructions for storage on the prescription label.

Conclusion

Communicating effective dosage instructions to patients clearly and succinctly is a responsibility of both the medical and pharmaceutical professions. Recent studies documenting the low order of compliance with prescription instructions indicate that poor communication between the medical and pharmaceutical professions and

The American Pharmaceutical Association and the American Society of Internal Medicine believe that the guidelines as stated above will serve as an initial step toward patients achieving a better understanding of their medication and dosing instructions. The two associations urge state and local societies representing pharmacists and prescribers to appoint joint committees for the purpose of refining these guidelines further as local desires and conditions warrant. The associations believe that such cooperative efforts between the professions are essential to good patient care and that significant progress can be made in other areas by initiating discussions between the two professions concerning common interests and goals.

* By American Pharmaceutical Association/American Society of Internal Medicine (revised March 1976).

Appendix B—Statement on Pharmacist-Conducted Patient Counseling*

It is well documented that safe and effective drug therapy most frequently occurs when patients are well informed about medications and their use. Knowledgeable patients exhibit increased compliance with drug regimens, resulting in improved therapeutic outcomes. Therefore, pharmacists, as well as other health professionals, have a responsibility to properly inform patients about their drug therapy.

Pharmacists' drug consultations with patients should be aimed at improving therapeutic outcomes by maximizing proper use of medications. Pharmacists, in conjunction with other health team members whenever possible, must make appropriate value judgements to determine the specific information and counseling required in each patient care situation.

Using suitable verbal, written or audio-visual communication techniques and methods, the pharmacist should inform, educate and counsel patients (or their representative or guardian) about the following items for each medication in the patient's drug regimen:

1. Name (trademark, generic, common synonym, or other descriptive name(s))
2. Intended use and expected action
3. Route, dosage form, dosage, and administration schedule
4. Special directions for preparation
5. Special directions for administration
6. Precautions to be observed during administration
7. Common side effects that may be encountered including their avoidance and action required if they occur
8. Techniques for self-monitoring of drug therapy
9. Proper storage
10. Potential drug-drug or drug-food interactions or other therapeutic contraindications
11. Prescription refill information
12. Action to be taken in the event of a missed dose
13. Any other information peculiar to the specific patient or drug

These thirteen points are applicable to non-prescription drugs as well as those ordered by a physician or other prescriber. In addition, pharmacists must counsel patients in the proper selection of non-prescription drugs as well as when and if they should be used.

* Approved by the Board of Directors, American Society of Hospital Pharmacists (November 17–18, 1975).

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