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CHAPTER 92

Oral Solid Dosage Forms

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

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

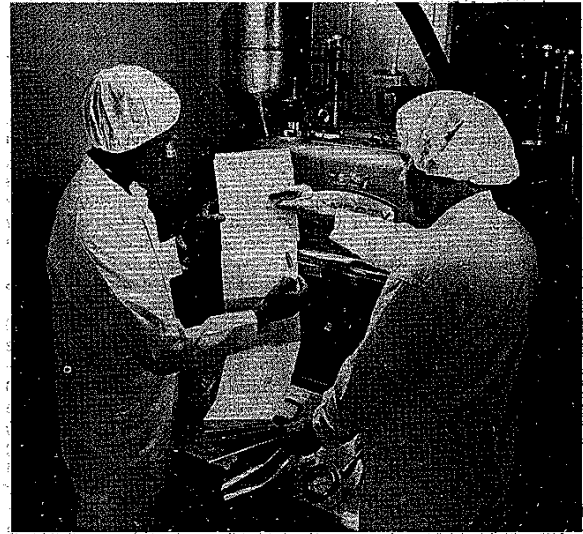


Fig 1. Tablet press operators checking batch record in conformance with Current Good Manufacturing Practices (courtesy, Lilly)

formulation but also on the raw materials, facilities, personnel, documentation, validated processes and equipment, packaging and the controls used during and after preparation (Fig 1).

Tablets

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

Although the basic mechanical approach for their manufacture has remained the same, tablet technology has undergone great improvement. Efforts are being made continually to understand more clearly the physical characteristics of powder compaction and the factors affecting the availability of the

drug substance from the dosage form after oral administration. Tableting equipment continues to improve both as to production speed and the uniformity of tablets compressed. Recent advances in tablet technology have been reviewed.²⁻¹³

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

Compressed Tablets (CT)

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

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

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

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

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

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

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 Drycoata*. Press-coated tablets also can be used to separate incompatible drug substances; in addition, they can provide a means to give an enteric coating to the core tablets. Both types of multiple-compressed tablets have been used widely in the design of prolonged-action dosage forms.

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

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

Compressed Tablets (CT)

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

The basic mechanical unit in all tablet-compression equipment includes a lower punch which fits into a die from the bottom and an upper punch, having a head of the same shape and dimensions, which enters the die cavity from the top after the tableting material fills the die cavity (see Fig 2). The tablet is formed by pressure applied on the punches and subsequently is ejected from the die. The weight of the tablet is determined by the volume of the material which fills the die cavity. Therefore, the ability of the granulation to flow freely into the die is important in insuring a uniform fill, as well as the continuous movement of the granulation from the source of

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

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

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

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

Molded Tablets or Tablet Triturates (TT)

Tablet triturates usually are made from moist material using a 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 originally were used for the preparation of solutions to be injected. Since stable parenteral solutions are now available for most drug substances, there is no justification for the use of hypodermic tablets for injection. Their use in this manner should be discouraged since the resulting solutions are not sterile. Large quantities of these tablets continue to be made, but for oral administration. No hypodermic tablets ever have been recognized by the official compendia.

supply or feed hopper. If the tablet granulation does not possess cohesive properties, the tablet after compression will crumble and fall apart on handling. As the punches must move freely within the die and the tablet must be ejected readily from the punch faces, the material must have a degree of lubrication to minimize friction and allow for the removal of the compressed tablets.

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

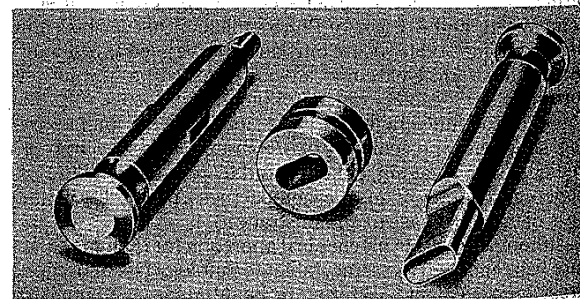


Fig 2. Basic mechanical unit for tablet compression: lower punch, die and upper punch (courtesy, Vector/Colton).

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

Tablet Ingredients

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

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

Diluents

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

processing to give them flowability and compressibility. These are discussed under *Direct Compression*, page 1626.

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

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

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

Binders

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

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

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

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