Shree H. N. Shukla Institute of Pharmaceutical Education and Research, Rajkot

B. Pharm
Semester-VI

Subject Name: Industrial Pharmacy-I
Subject Code: BP605TP

UNIT.2: Tablet

- **Definition:**
  According to the USP, tablets are solid dosage forms, containing medicinal substances with or without suitable diluents. They may be classed, according to the method of manufacture, as compressed tablets or molded tablets.
  Tablets are solid dosage forms consisting of active pharmaceutical ingredient and suitable excipients. They may vary in size, shape, weight, hardness, thickness, disintegration and dissolution characteristics, and in other aspects.

- **Advantages:**
  1. They are single unit dosage forms so and convenient to use.
  2. They are having more stability than other dosage forms.
  3. Tablets provide stable and an accurately measured dosage of drug substance to patients.
  4. Tablets can be formulated to protect drugs which are unstable in gastric environment (enteric coating).
  5. Tablets are cost effective to manufacture also to the patients.
  6. The drugs which are having unpleasant taste can be masked which increase patient compliance.
  7. Tablet may be easily manufactured to show product identification using colored coating, embossed markings and printing.
  8. Tablets may be designed to release the drug at controlled rate and desired site.

- **Disadvantages:**
  1. The product loss is more as it involves number of process like weighing, milling, drying, mixing etc.
  2. Chances of patient to patient variations are more as release and absorption of drug from tablet is dependent on physiological factors such as gastric resident/ emptying time.
  3. The substances which are having poor compression properties are difficult to convert in to tablets.
  4. Geriatric and pediatrics patients feel difficulties while swallowing the tablets.
  5. Tablets cannot be administered to unconscious patients.

- **Ideal characteristics of Tablets:**
  1. A tablet must be strong and hard to withstand mechanical shock during packing, shipping, dispensing and use.
  2. The drug release from the tablet should be predictable and reproducible.
  3. The tablet must be chemically and physically stable to maintain its chemical and physical attributes during manufacture, storage and use.
  4. Tablet must be uniform in weight and in drug content.
  5. The tablet should be elegant and should be free from defects like cracks, discoloration, chips etc.

- **Classification of Tablets OR Types of Tablets**
  Tablets can be classified according to route of administration

a) Tablets ingested orally

1. Compressed tablet
2. Multiple compressed tablet
    a. Compression coated tablets
    b. Layered tablets
    c. Inlay tablets
3. Delayed release tablet
4. Sugar coated tablet
5. Film coated tablet
6. Chewable tablet

b) Tablets released their content in oral cavity

1. Buccal tablet
2. Sublingual tablet
3. Troches or lozenges
4. Dental cone

c) Tablets used to prepare solution

1. Effervescent tablet
2. Dispensing tablet
3. Hypodermic tablet
4. Tablet triturates

d) Tablet ingested by other route

1. Implantation tablet (implants)
2. Vaginal tablet

Tablets can be classified according to coating

a. Uncoated tablet

b. Coated tablet

1. Film coated
2. Sugar coated
3. Enteric coated

Compressed tablet (CT)

Compressed tablets are formed by compression and, in their simplest form, 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. The vast majority of tablets commercialized today are compressed tablets, either in an uncoated or coated state.

Sugar-Coated Tablets (SCT)

Sugar-coated tablets are compressed tablets surrounded by 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. These coatings were once quite common, but lost commercial appeal due to the high cost of process validation. Recently, they have made a comeback, due to patient popularity and technical advances.

Film-Coated Tablets (FCT)

Film-coated tablets are compressed tablets 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 the greatly reduced time required for the coating operation. Advances in material science and polymer chemistry have made these coatings the first choice of formulators.

Enteric-Coated Tablets (ECT)

Enteric-coated tablets 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 inactivated or destroyed in the stomach, for those that irritate the mucosa, or as a means of delayed release of the medication.

Multiple Compressed Tablets (MCT)

Multi-compressed tablets are compressed tablets made by more than one compression cycle. This process is best used when separation of active ingredients is needed for stability purposes or if the mixing process is inadequate to guarantee uniform distribution of two or more active ingredients.

Layered Tablets

Layered 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 more layers.

Press-Coated Tablets

Press coated tablets, also referred to as dry-coated tablets, 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), while retaining the attributes of sugarcoated 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 of giving an enteric coating to the core tablets. Both types of multiple-compressed tablets have been widely used in the design of prolonged-action dosage forms.

Controlled-release Tablets (CRT)

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 that 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. Other names for these types of tablets are; Extended Release, Sustained Release, Prolonged Release, Delayed Release, and, in the case of pulsatile tablets, Repeat Action, Pulsatile Release, or Pulse Release.

Tablets for Solution (CTS)

Compressed tablets used for preparing solutions or imparting given characteristics to solutions must be labeled to indicate 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, effervescent tablets contain sodium bicarbonate and an organic acid, such as tartaric or citric. In the presence of water, these additives react, liberating carbon dioxide that acts as a disintegrator 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 by means other than swallowing, the label must indicate the manner in which it is to be used.

Buccal and Sublingual Tablets

Buccal and sublingual tablets are small, flt, oval tablets. Tablets intended for Buccal administration by inserting into the Buccal pouch (the space between the lip and gum in the mouth) 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 have employed materials that act as bioadhesives to increase absorption of the drug. Other 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 erythrityl tetranitrate, are placed under the tongue. Sublingual tablets dissolve rapidly, and the drug substances are absorbed readily by this form of administration.

Lozenges

Lozenges are tablets that dissolve slowly in the mouth and so release the drug dissolved in the saliva.
Lozenges are used for local medication in the mouth or throat, e.g. with local anaesthesia, antiseptic and antibiotic drugs. They can thus be described as slowrelease tablets for local drug treatment. Disintegrants are not used in the formulation, but otherwise such tablets are similar in composition to conventional tablets. In addition, lozenges are often coloured and include a flavour. The choice of filler and binder is of particular importance in the formulation of lozenges, as these excipients should contribute to a pleasant taste or feeling during tablet dissolution. The filler and binder should therefore be water soluble and have a good taste. Common examples of fillers are glucose, sorbitol and mannitol. A common binder in lozenges is gelatin. Lozenges are normally prepared by compaction at high applied pressures in order to obtain a tablet of high mechanical strength and low porosity which can dissolve slowly in the mouth.

Molded tablets or tablet triturates (TT)

Tablet triturates are usually made from moist material, using a triturate mold that 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)

Dispensing 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

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)

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 (GI) fluids and controlled-release polymers designed to slow 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 that is to be compressed into tablets. The basic mechanical unit in all tablet-compression equipment includes a lower punch that fits into a die from the bottom and an upper punch, with a head of the same shape and dimensions, which enters the die cavity from the top, after the tableting material fills the die cavity (Fig. 1).

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 that fills the die cavity. Therefore, the ability of the granulation to flow freely into the die is important in ensuring a uniform fill, as well as the continuous movement of the granulation from the source of supply or feed hopper. If the tablet granulation does not possess cohesive properties, the tablet, after compression, will crumble and fall apart on handling. As the punches must move freely within the die and the tablet must be ejected readily from the punch faces, the material must have a degree of lubrication to minimize friction and allow the removal of the compressed tablets.

There are three general methods typically used for commercial tablet preparation: the wet-granulation method, the dry granulation method, and direct compression. The method of preparation and the added ingredients are selected to give the tablet formulation the desirable physical characteristics, allowing the rapid compression of tablets.

After compression, the tablets must have a number of additional attributes, such as appearance, hardness, disintegration ability, appropriate dissolution characteristics, and uniformity, which are also influenced by both the method of preparation and the added materials present in the formulation. In the preparation of compressed tablets, the formulator must also be cognizant of the effect that 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, so 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. Conversely, literature reports indicate that the reformulation of a commercial digoxin tablet resulted in a tablet that, although containing the same quantity of drug substance, 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.

Figure -1. Multi-tip punches and die.

QUALITY ATTRIBUTES OF TABLETS

Like all other dosage forms, tablets should fulfill a number of specifications regarding their chemical, physical and biological properties. Quality issues relating to the final product are worth considering early in the development process) as they give an indication of the goal to be achieved during the development and manufacture of tablets. Tests and specifications for some of these properties are given in pharmacopoeias. The most important of these are dose content and dose uniformity, the release of the drug in terms of tablet disintegration and drug dissolution, and the microbial quality of the preparation. In addition, the authorities and manufacturers define a set of other specifications. One such important property is the resistance of the tablet towards attrition and fracture.

The quality attributes a tablet must fulfill can be summarized as follows:

1. The tablet should include the correct dose of the drug.

2. The appearance of the tablet should be elegant and its weight, size and appearance should be consistent.

3. The drug should be released from the tablet in a controlled and reproducible way.

4. The tablet should be biocompatible, i.e. not include excipients, contaminants and microorganisms that could cause harm to patients.

5. The tablet should be of sufficient mechanical strength to withstand fracture and erosion during handling.

6. The tablet should be chemically, physically and microbiologically stable during the lifetime of the product.

7. The tablet should be formulated into a product acceptable by the patient.

8. The tablet should be packed in a safe manner

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 fist group contains those that 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, surfactants, colors, and, in the case of chewable tablets, flavors and sweetening agents, and, in the case of controlled release tablets, polymers or hydrophobic materials, such as waxes or other solubility-retarding materials. In some cases, antioxidants or other materials can be added to improve stability and shelf-life. Although the term "inert" has been applied to these added materials, it has become apparent that there is an important relationship between the properties of the excipients and the dosage forms containing them.8 Preformulation studies demonstrate their influence on stability, bioavailability, and the processes by which the dosage forms are prepared.

Diluents

Frequently, the single dose of the active ingredient is small, and an inert substance is added to increase the bulk to make the tablet a practical size for compression. Diluents are like 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 suffiient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing.

Binders

Agents used to impart cohesive qualities to the powdered material are referred to as binders or granulators. They impart cohesiveness to the tablet formulation that ensures the tablet remain intact after compression, as well as improve the free-flowing qualities by the formulation of granules of desired hardness and size. Materials commonly used as binders include starch, gelatin, and sugars, such as sucrose, glucose, dextrose, molasses, and lactose. Natural and synthetic gums that 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 considered binders under certain circumstances are polyethylene glycol, ethylcellulose, waxes, water, and alcohol. Synthetic binders, such as polyvinylpyrrolidone and HPMC are becoming more popular. The quantity of binder used has considerable inflence on the characteristics of the compressed tablets. The use of too much binder or too strong a binder will make a hard tablet that will not disintegrate easily and will cause excessive wear of punches and dies. Materials that have no cohesive qualities of their own require a stronger binder than those with these qualities. Alcohol and water are not binders in the true sense of the word, but, due to 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. Starch paste, gelatin solution and cellulosic solution used as binder in solution form.

Lubricants

Lubricants have a number of functions in tablet manufacture. They prevent adhesion of the tablet material to the surface of the dies and punches, reduce interparticle friction, facilitate the ejection of the tablets from the die cavity, and may improve the rate of flw of the tablet granulation. Commonly used lubricants include talc, magnesium stearate, calcium stearate, stearic acid, glyceryl behanate, hydrogenated vegetable oils, and polyethylene glycol (PEG). Most lubricants, with the exception of talc, are used in concentrations below 1%. When used alone, talc may require concentrations as high as 5%.

Glidants

A glidant is a substance that improves the flow characteristics of a powder mixture. These materials always are

added in the dry state just prior to compression (i.e., during the lubrication step). Colloidal silicon dioxide Cab-o-sil (Cabot) is the most commonly used glidant and is used in low concentrations of 1% or less. Talc (asbestos-free) is also used and may serve the dual purpose of lubricant glidant. It is especially important to optimize the order of addition and the mixing process for these materials, to maximize their effect and to make sure their influence on the lubricant(s) is minimized.

Disintegrants

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

Starch has a great affiity 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%.

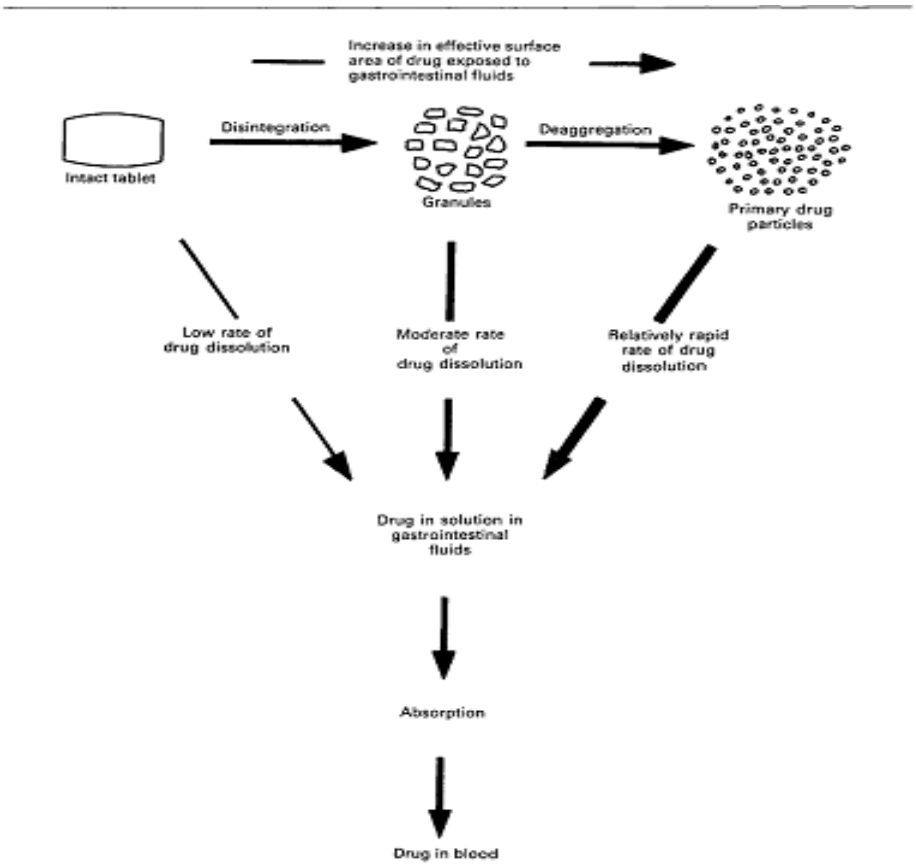


Fig.2 Mechanism of drug release from tablet

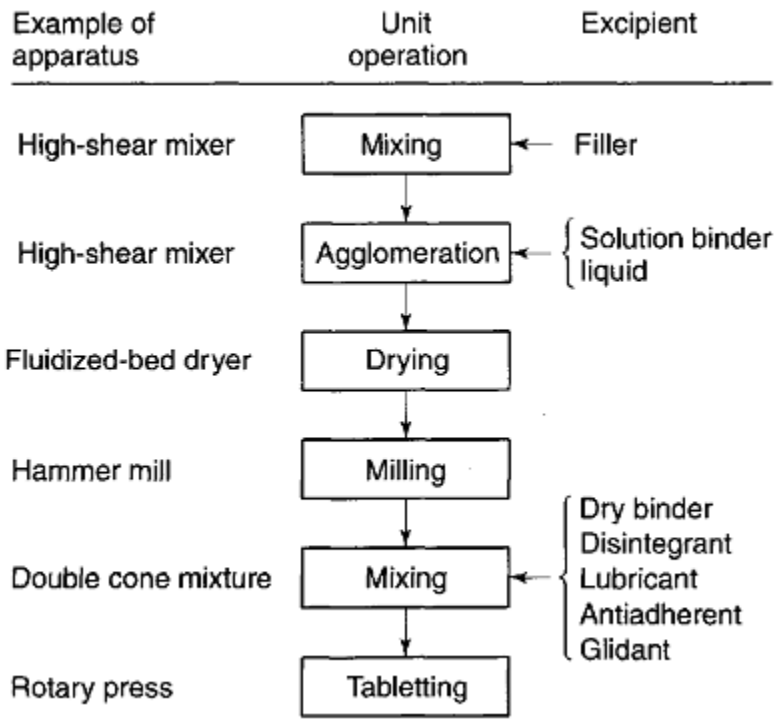
Coloring agents

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

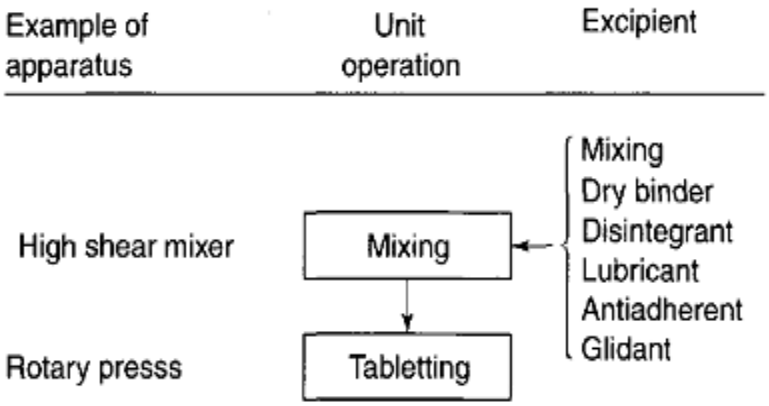
Flavoring agents

In addition to the sweetness that 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 used widely. With the banning of the cyclamates and the indefinite status of saccharin, new natural sweeteners are being sought. Aspartame, has found applications in pharmaceutical formulations. Sweeteners, other than the sugars, have the advantage of reducing the bulk volume, considering the quantity of sucrose required to produce the same degree of sweetness. Present in small quantities, they do not markedly affect the physical characteristics of the tablet granulation.

GRANULATION METHODS



Overview of sequence of unit operations used in the production of tablets with precompression treatment by granulations.



Overview of sequence of unit operations used in the production of tablets by direct compression

Wet granulation

The most widely used and most general method of tablet preparation is the wet-granulation method. Its popularity is due to the greater probability that the granulation will meet all the physical requirements for the compression of good tablets. Its chief disadvantages are the number of separate steps involved, as well as the time and labor necessary to carry out the procedure, especially on a large scale.

The steps in the wet method are weighing, mixing, wet massing, screening the damp mass, drying, dry screening, lubrication, and compression. The equipment involved depends on the quantity or size of the batch and the percent active ingredient per total weight of the tablets. Wet massing can be performed by:

1. Low Shear mixers/granulators,
2. High Shear mixers/granulators,
3. Fluid-Bed granulators/dryers,
4. Spray Dryers, or
5. Extruders and Spheronizers.

Low shear mixers include the barrel, cube, twin shell, double cone, slated double cone, ribbon, sigma blade, planetary mixers, etc. (Fig.-3). Although these mixers continue to be used in some older pharmaceutical factories, they are replaced, now, by the high shear mixers/granulators. High shear mixers are stationary shell mixers with a large mixer scraper blade, which mixes the ingredients, eliminates dead spots, and presents the ingredients with a high speed chopper blade, which intimately

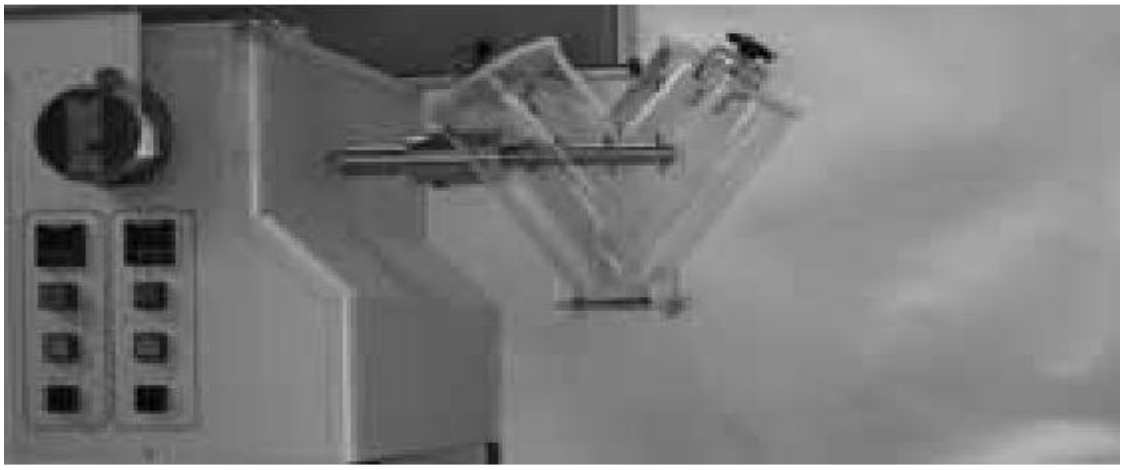


Figure-3 Twin Shell Blender with Intensifier Bars.

mixes the ingredients and breaks the lumps. The advantages of the high shear mixers/granulators are: simple, robust technology, production of high density granules, rapid and efficient mixing, low liquid requirements, and equipped for drying. There are many models/trade names of high shear mixers in the pharmaceutical market, such as the Loedige, Littleford MGT, Diosna, Fiedler, Vector, Glatt, GEA, and Hüttlin Gentlewing. (Figure-4) shows a typical high shear mixer granulator from Vector, and (Figure 5) shows a typical Glatt high shear mixer. A relatively new high shear mixer from Hüttlin is the Gentlewing High Shear Mixer, which is available in laboratory and large scale sizes, either top driven or bottom driven. The Gentlewing technology applies the principle of a positive displacement impeller for blending a non-Newtonian medium.

Figure -4. Vector High Shear Mixer.

Figure -5. High Shear Mixer. (Courtesy of GLATT.)

The impeller shape matches the contour of the mixing container, and its angled impeller plate ensures a forced mixing of the product. Rather than using the impulse of an impeller for mixing, the Gentlewing's uniform presence throughout the product container distributes the mixing energy, at lower speeds but higher torque, evenly throughout the product, reducing segregation issues typically caused by high dynamic forces (Fig.-6 and Fig.-7).

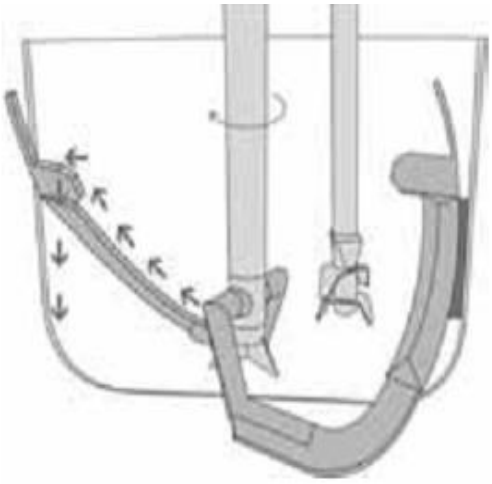


Figure-6 . Gentlewing High Shear Mixer, diagram.

Figure-7. Gentlewing High Shear Mixer.

The active ingredient, diluent, and part of the disintegrant are mixed or blended well. Solutions of the binding agent are added or sprayed 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 over-wetted, 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. In modern high shear mixers, the end point of wet granulation is no more dependent on the experience of the operator and the "hand" feeling of the wet mass, but is measured accurately by a built in torque meter. This consistency and reproducibility from batch to batch are assured. The wet granulation mass is then forced through a 6- or 8-mesh screen. Small batches can be forced through by hand, using a manual screen. For larger quantities, one of several comminuting mills suitable for wet screening can be used. These include the Stokes oscillator, Colton rotary granulator, Fitzpatrick comminuting mill, Cone Mill, or Stokes tornado mill. In comminuting mills, the granulation is forced through the sieving device by rotating hammers, knives, or oscillating bars (Fig-8 –10).

Figure-8 Fitz mill Comminutor

Figure-9 Hammers

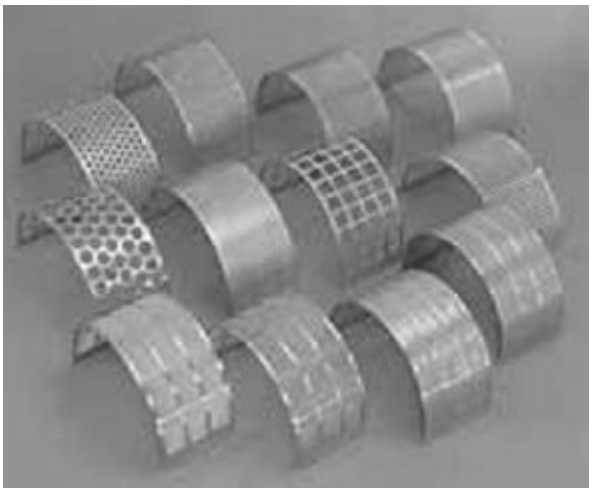


Figure-10 Screens

Most high-speed mixers are equipped with a chopper blade that operates independently of the main mixing blades and can replace the wet milling step (i.e., can obviate the need for a separate operation).

For tablet formulations in which continuous production is justified, extruders, such as the Reitz extruder, have been adapted for the wet-granulation process. Moist material from the wet milling step, traditionally, was placed on large sheets of paper on shallow wire trays and placed in drying cabinets with a circulating air current and thermostatic heat control. Although tray drying was the most widely used method of drying tablet granulations in the past, fluid-bed drying is now considered the standard. In drying tablet granulation by fluidization, the material is suspended and agitated in a warm air stream, while the granulation is maintained in motion.

Drying tests comparing the fluidized bed and a tray dryer for a number of tablet granulations indicated that the former was 15 times faster than the conventional method of tray drying. In addition to the decreased drying time, the fluidization method is claimed to have other advantages, such as better control of drying temperatures, decreased handling costs, and the opportunity to blend lubricants and other materials into the dry granulation directly in the fluidized bed (Fig.11).

Figure-11. Schematic Fluid bed Dryer

The application of microwave drying and infrared drying to tablet granulations has been reported as successful for most 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 Novartis 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, due to the moving bed, controlled temperature, and 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. Recently, many machine manufacturers, such as Hüttlin, GEA, and Glatt, introduced the single pot technology in which the drying process can also take place in a vertical granulator specially equipped for this purpose. The drying is assisted by suitable measures, according to the product and the process, such as heated wall surfaces, gas stripping, and vacuum (Fig. 12).

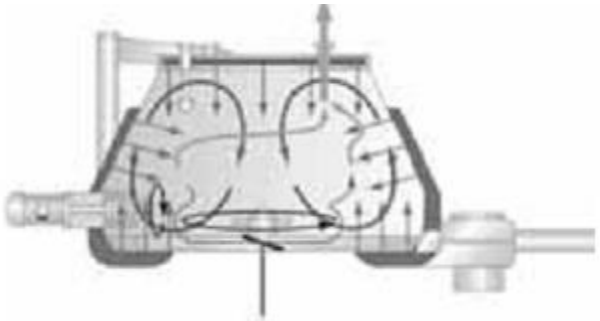


Figure-12. Single Pot Vertical Granulator.

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 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 selected depends on the diameter of the punch. The following sizes are suggested:

1. Tablets up to 3/16 inch diameter, use 20-mesh
2. Tablets 7/32 to 5/16 inch, use 16-mesh
3. Tablets 11/32 to 13/32 inch, use 14-mesh
4. Tablets7/16 inch and larger, use 12-mesh

For small amounts of granulation, hand screens may be used and the material passed through with the aid of a stainless steel spatula. With larger quantities, any of the comminuting mills with screens corresponding to those just mentioned may be used. Note that the smaller the tablet, the finer the dry granulation to enable more uniform filing 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 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 screened onto the granulation through 60- or 100-mesh nylon cloth to eliminate small lumps, as well as to increase the covering power of the lubricant. As it is desirable for each granule to be covered with the lubricant, the lubricant is blended with the granulation very gently, preferably in a blender using a tumbling action, such as the Patterson Kelly Twin Shell Blender (Fig. 3). Gentle action is desired to maintain the uniform granule size, resulting from the granulation step. It has been claimed that too much fie 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 blowout around the upper punch and down past the lower punch, making it necessary to clean the machine frequently. Fines, however, at a level of 10–20%, are, traditionally, sought by the tablet formulator. The presence of some fines is necessary for the proper filing of the die cavity.

Now, even higher concentrations of fines are used successfully in tablet manufacture. Most investigators agree that no general limits exist for the amount of fines that can be present in a granulation; it must be determined for each specific formula. Many formulators once believed (and some still believe) that over blending resulted in an increased amount of fines and, hence, caused air entrapment in the formula. The capping and laminating of tablets associated with over blending lubricants was thought to be caused by

these air pockets. Most scientists now recognize that a more plausible explanation has to do with the function of the lubricants themselves. Since the very nature of a lubricant tends to make surfaces less susceptible to adhesion, over blending prevents the intergranular bonding that takes place during compaction.

Fluid-bed granulation

A relatively new method for granulating evolved from the fluid bed drying technology previously described. The concept was to spray a granulating solution onto the suspended particles, which then would be dried rapidly in the suspending air. The main benefit from this system is the rapid granulation and drying of a batch. The main fims that developed this technology are Glatt, Aeromatic (now GEA), Vector, and Hüttlin. The general design of these systems is the same with most companies (Fig. 13–16).

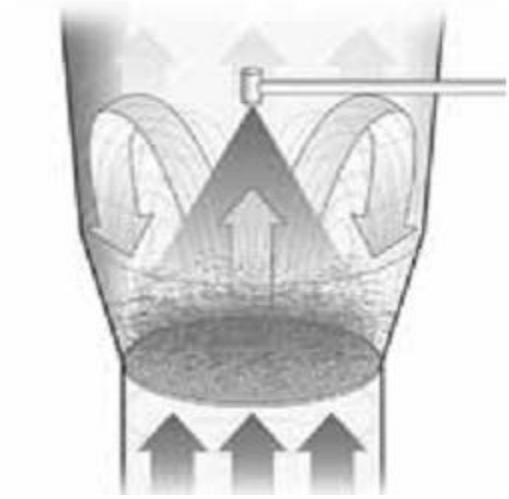


Figure-13 . Fluid Bed Top Spray Granulator.

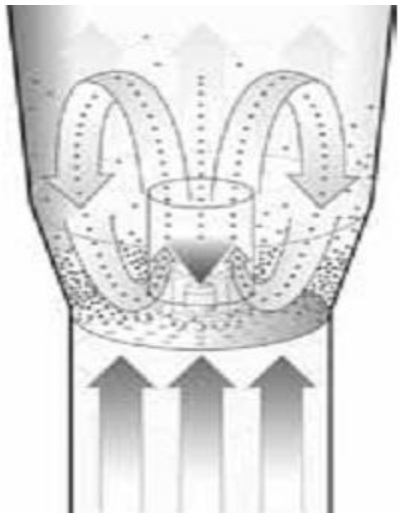


Figure-14. Bottom Spray Fluid Bed.

Figure-15. Tangential Spray Fluid Bed

Figure -16. Fluid-Bed.

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 ready for compression after the addition of the lubricant. An obvious advantage exists, since granulating and drying can take place in a single piece of equipment. It should be noted, however, that many of the mixers discussed previously can be supplied with a steam jacket and vacuum and can provide the same advantage. In these systems, a granulating solution or solvent is sprayed into or onto the bed of suspended particles. The rate of addition of the binder, temperature in the bed of particles, temperature of the air, volume, and moisture of the air all play an important role in the quality and performance of the final product. Many scientists feel that this method is an extension of the wet-granulation method, as it incorporates many of its concepts. However, anyone who has developed a formulation in a fluid-bed system knows that the many operating parameters involved make it somewhat more complex. In addition to its use for the preparation of tablet granulations, this technique has also been proposed for the coating of solid particles, as a means of improving the flow properties of small particles. Researchers have observed that, in general, fluid-bed granulation yields a less dense particle than conventional methods, and this can affect subsequent compression behavior. The Merck facility at Elkton, VA, was the first completely automated tablet production facility in the world. The entire tablet-manufacturing process, based on a wet-granulation method, was computer controlled. The system weighed the ingredients, blended, granulated, dried, and lubricated to prepare a uniform granulation of specified particle size and particle-size distribution. The computer directed the compression of the

material into tablets with exacting specifications for thickness, weight, and hardness. After compression, the tablets were coated with a water-based film coating. The computer controlled and monitored all flow of material. The plant represented the fist totally automated pharmaceutical manufacturing facility. However, due to shifting market trends, the burdens of process validation, and changes to processes, totally automated processes are, generally, not used today. Instead, many production operations focus on computer-controlled and monitored unit operations, such as seen in various tableting machines and granulators.

Equipment suppliers work closely with individual pharmaceutical companies in designing specialized and unique systems. Newer developments from the machine manufacturing industries improved the process efficiency by modifying the air distribution plate and introducing the new Diskjet with a tangential air exit, which ensures optimum exchange of materials and energy, as well as reduced process time for drying, granulating, and coating (Fig. 17).

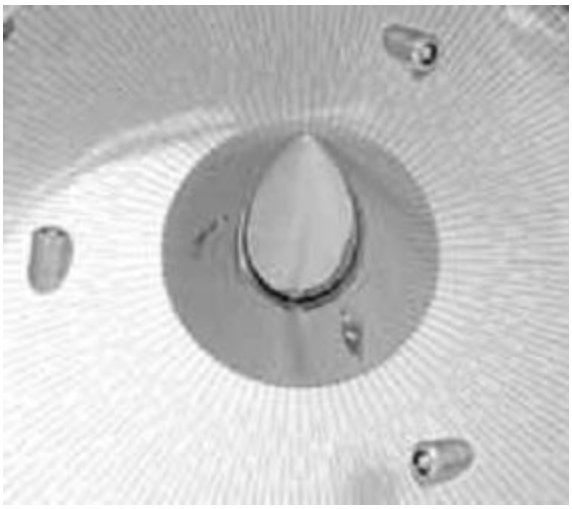


Figure-17. Disk Jet.

Thus, a high shear mixer is connected to a cone mill and then a fluid bed dryer. Charging and discharging take place under totally dust and contamination free conditions (Fig.18).

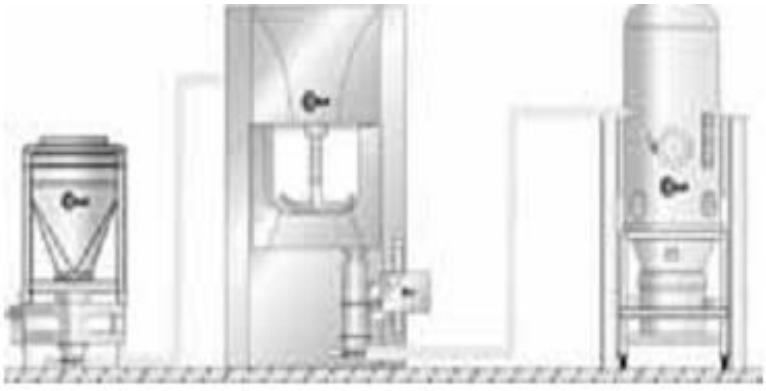


Figure-18. Horizontal granulation line consisting of a Top Driven Granulator and a Fluid bed Dryer.

Dry granulation

When tablet ingredients are sensitive to moisture or are unable to withstand elevated temperatures during drying and when the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form granules. This method is referred to as dry granulation, precompression, or double compression. It eliminates a number of steps but still includes weighing, mixing, slugging, dry screening, lubrication, and compression.

The active ingredient, diluent (if 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 fie powders flow better into large cavities. Also, producing large slugs decreases production time: 7/8-1 in are the most practical sizes for slugs. Sometimes, to obtain the pressure 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 and blended gently, and the material is compressed into tablets. Aspirin is a good example of where slugging is satisfactory.

Other materials, such as aspirin combinations, acetaminophen, 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 densified passes between high-pressure rollers that 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 that may be required to obtain cohesion of certain materials may result in a prolonged dissolution rate. Compaction mills available include the Chilsonator (Fitzpatrick), Roller Compactor (Vector), and the Compactor Mill (Fig. 19).

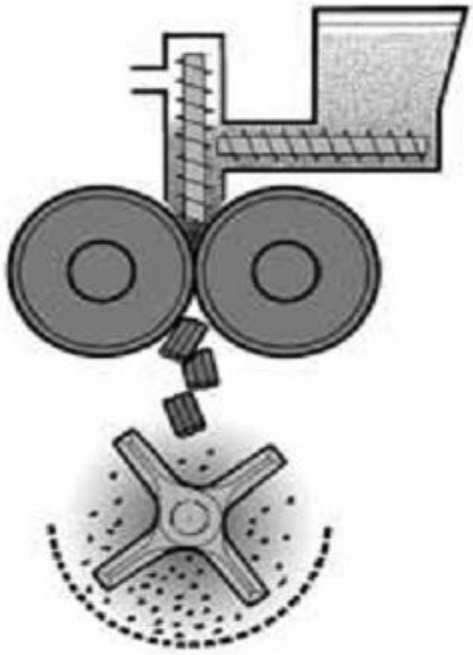


Figure-19. Roller Compactor Granulator.

Direct Compression

As its name implies, direct compression consists of compressing tablets directly from component materials, without modifying the physical nature of the materials themselves. 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, and permanganate), ammonium chloride, and methenamine. These materials possess cohesive and flow properties that make direct compression possible. Since the pharmaceutical industry is constantly making efforts to increase the efficiency of tableting operations and reducing costs by using the smallest amount of floor space and labor as possible for a given operation, increasing attention is given to this method of tablet preparation. Approaches used to make this method more universally applicable include the introduction of formulation additives capable of imparting the characteristics required for compression and the use of force feeding devices to improve the flow of powder blends.

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

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

Compressible sugar consists mainly of sucrose that is processed to have properties suitable for direct compression. It also may contain small quantities of dextrin, starch, or invert sugar. It is a white crystalline powder with a sweet taste and complete water solubility. It requires the incorporation of a suitable lubricant at normal levels for lubricity. The sugar is used widely for chewable vitamin tablets because of its natural sweetness. One commercial source is Di-Pac (Amstar), prepared by the 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 mouth feel, resulting from its negative heat of solution. In its granular form (lCI Americas), it has good flow and compressible qualities. It has low moisture content and is not hygroscopic. The excipient that has been studied extensively as a direct compression vehicle is microcrystalline cellulose (Avicel, FMC). This non-fibrous form of cellulose is obtained by spray-drying washed, acid-treated cellulose and is available in

several grades, ranging in average particle size from 20 to 250 um. 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 than other excipients. Recently, FMC introduced Avicel DG, which occurs as a white, odorless powder, containing 75% of microcrystalline cellulose and 25% anhydrous dibasic calcium phosphate. The wet dispersion and spray-drying of microcrystalline cellulose and anhydrous dibasic calcium phosphate results in an intimate physical combination, which cannot be achieved by traditional dry blending. JRS PHRMA introduced PROSOLV, which is coprocessed silicified microcrystalline cellulose. JRS PHARMA also introduced to the pharmaceutical excipient market PROSOLV EASY TAB, which is composed of coprocessed microcrystalline cellulose, colloidal silicon dioxide, sodium starch Glycolate, and sodium stearyl fumarate, which is claimed to be the ideal direct compression complete excipient.

Forced-flow feeders are mechanical devices, available from pharmaceutical equipment manufacturers, designed to deaerate light and bulky material. Mechanically, they maintain a steady flow of powder moving into the die cavities under moderate pressure. By increasing the density of the powder, higher uniformity in tablet weights is obtained (Fig.-20,21). Recently, many companies have reversed their optimism for some direct-compression systems. Some formulations made by direct compression were not as forgiving as the older, wet-granulated products were. As raw material variations occurred, especially with the drug, many companies found themselves with poorly compactable formulations. Interest in direct compression is also stimulating basic research on the flowability of powders with and without additives

Figure 20. Forced Flow Feeder.

Figure-21. Forced Flow Feeder.

POWDER COMPACTION

Compressed tablets became a commercially viable and efficient dosage form with the invention of tablet machines. In 1843, William Brockendon, a British inventor, author, artist, and watchmaker, received British Patent #9977 for Shaping Pills, Lozenges, and Black Lead by Pressure in Dies. In over 150 years of tablet manufacture, the basic process has not changed. Surprisingly, improvements have been made only with regards to speed of manufacture and quality control. The process of compaction has several identifiable phases. As can be seen in Figure -3, when powders undergo compression (a reduction in volume), the first process to occur is a consolidation of the powders. During this consolidation phase, the powder particles adopt a more efficient packing order. The second phase of the compaction process is elastic or reversible deformation. If the force were removed during this phase, the powder would completely recover to the efficiently packed state. For most pharmaceutical powders, this phase is very short in duration and very difficult to identify on most instrumented tablet presses. The third phase of compaction is plastic, or irreversible, deformation of the powder bed. It is this phase that is the most critical in tablet formation. If too much force is applied to the powder, brittle fracture occurs.

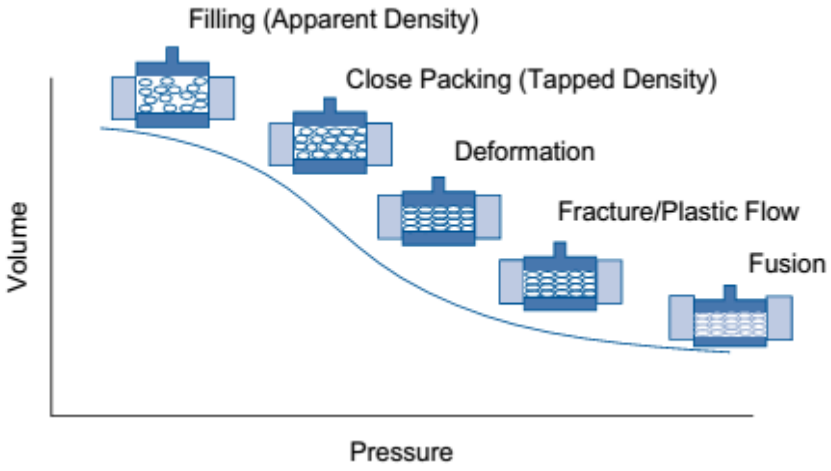


Figure-22. The stages of powder compaction.

TABLET MANUFACTURING

Stages in tablet formation

Tablets are prepared by forcing particles into close proximity to each other by powder compression, which enables the particles to cohere into a porous, solid specimen of denned geometry. The compression takes place in a die by the action of two punches, the lower and the upper, by which the compressive force is applied. Powder compression is denned as the reduction in volume of a powder owing to the application of a force. Because of the increased proximity of particle surfaces accomplished during compression, bonds are formed between particles which provides coherency to the powder, i.e. a compact is formed. Compaction is denned as the formation of a porous specimen of denned geometry by powder compression.

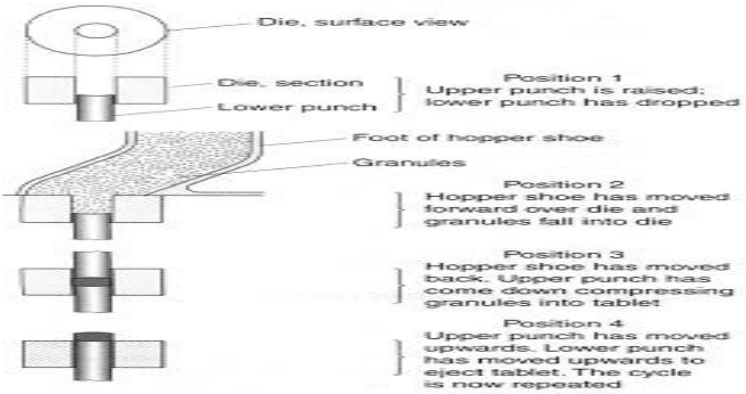


Fig. 23 The sequence of events involved in the formation of tablets

The process of tabletting can be divided into three stages (sometimes known as the compaction cycle) (Fig.23).

Die filllng

This is normally accomplished by gravitational flow of the powder from a hopper via the die table into the die (although presses based on centrifugal die filling are also used). The die is closed at its lower end by the lower punch.

Tablet formation

The upper punch descends and enters the die and the powder is compressed until a tablet is formed. During the compression phase, the lower punch can be stationary or can move upwards in the die. After maximum applied force is reached, the upper punch leaves the powder, i.e. the decompression phase.

Tablet ejection

During this phase the lower punch rises until its tip reaches the level of the top of the die. The tablet is subsequently removed from the die and dies table by a pushing device.

Tablet presses

There are two types of press in common use during tablet production: the single-punch press and the rotary press. In addition, in research and development work hydraulic presses are used as advanced equipment for the evaluation of the tabletting properties of powders and the prediction of scale-up on the

properties of the formed tablets (scale-up refers to the change to a larger apparatus for performing a certain operation on a larger scale).Single-punch press (eccentric press) A single-punch press possesses one die and one pair of punches (Fig. 24). The powder is held in a hopper which is connected to a hopper shoe located at the die table. The hopper shoe moves to and fro over the die, by either a rotational or a translational movement. When the hopper shoe is located over the die, the powder is fed into the die by gravity. The amount of powder filled into the die is controlled by the position of the lower punch. When the hopper shoe is located beside the die, the upper punch descends and the powder is compressed. The lower punch is stationary during compression and the pressure is thus applied by the upper punch and controlled by upper punch displacement.

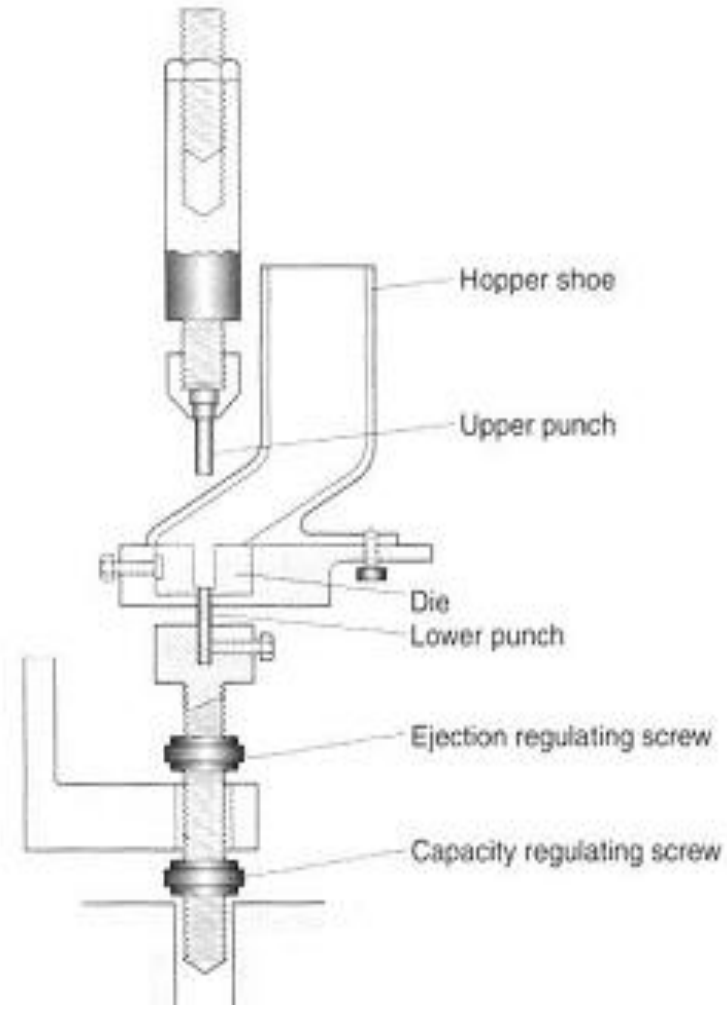


Fig. 5 A single punch tablet press

Rotary Tablet machines

For increased production, rotary machines offer great advantages. A head carrying a number of sets of punches and dies revolves continuously, while the tablet granulation runs from the hopper, through a feed frame, and into the dies placed in a large, steel plate revolving under it. This method promotes a uniform fill of the die and, therefore, an accurate weight for the tablet.

Compression takes place as the upper and lower punches pass between a pair of rollers, as can be seen in Figure-25.

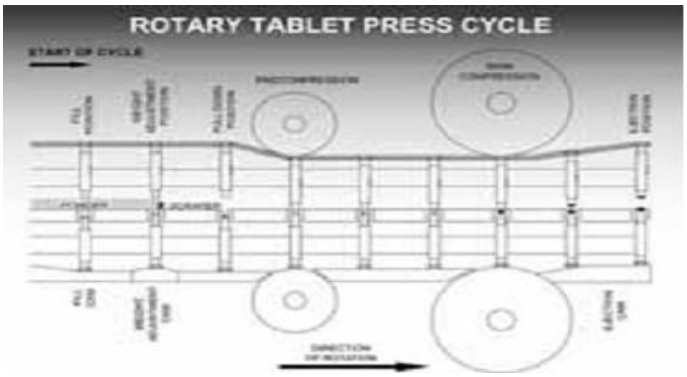


Figure-25. Rotary Tablet Press Cycle.

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. One of the factors that contributes to the variation in tablet weight and hardness during compression is the internal flow of the granulation within the feed hopper.

On most rotary machine models, there is an excess pressure release that 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 to insert different sets to produce a great variety of sizes and shapes.

Most rotary tablet presses measure a tablet's weight either by measuring its variation in tablet height at precompression or by the force at main compression. They compress a volume of granules, captured in a die, between two rollers, using an upper and lower punch. By changing the distance between the rollers, one adjusts the force used to compress tablets. Once the distance between the rollers is set, the compression force will stay the same. Several factors affect the precise amount of granules captured within each die. For example, granule size, size distribution, and variation in punch length can have an effect. In addition, an excessively high rotational speed allows the granules insufficient time to fall into the die. Variations in the amount of granules in each die result in tablets of different weights and densities. An inconsistency in the maximum compression force can result in inconsistent tablet properties, thus, affecting the efficacy of the dosage form. Compression to equal force (EF) is a new concept that allows tablets

to be compressed at the same peak compression force, independent of tablet weight. This method relies on the use of an air piston (Fig.-26).

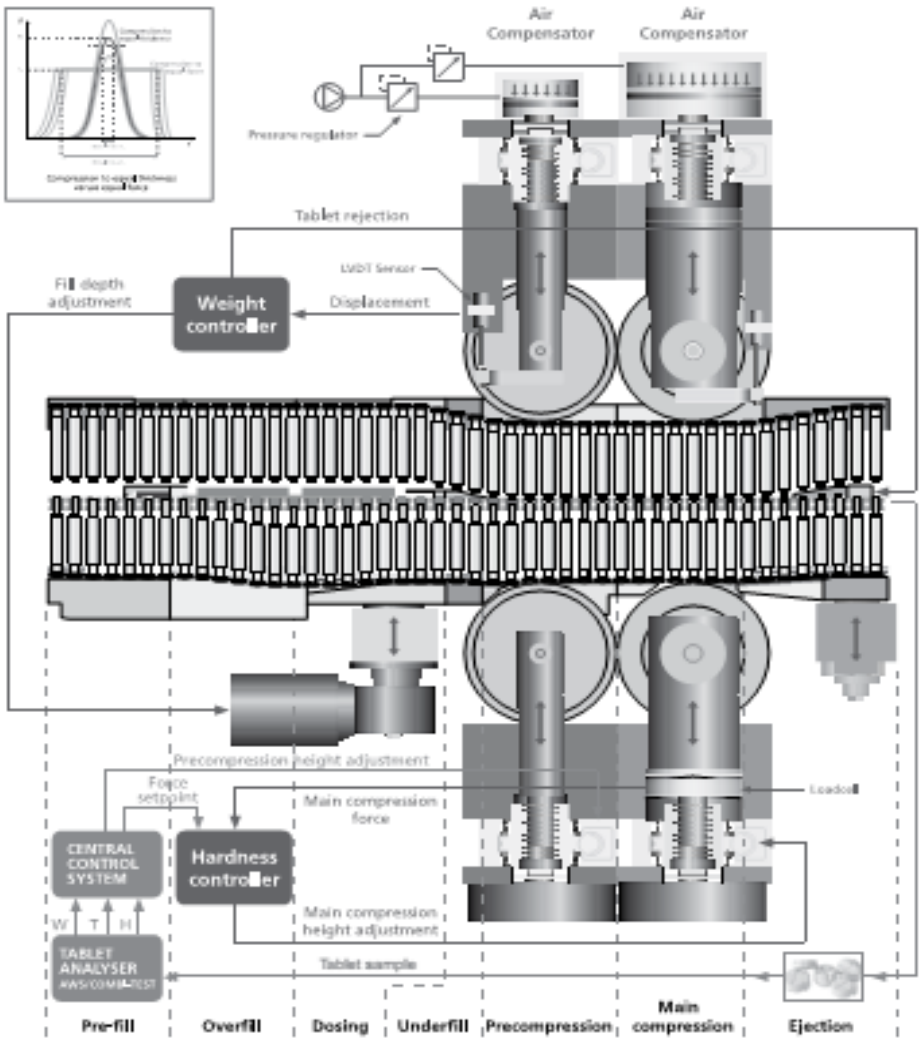


Figure-26. Rotary Tablet Compression Cycle

The air piston is installed at the precompression and main compression station and allows the pre- and main compression rollers to be floating rather than fixed. The piston moves vertically in a cylinder filled with compressed air. The air pressure in the cylinder is preset and kept constant by a pressure regulating valve and an expansion chamber. Because the surface of the cylinder and the air pressure are constant, the force is also constant, irrespectively of the position of the floating roller. If the air pressure in the cylinder is such that this maximum compression force is higher than the actual compression force, the system compresses tablets to equal thickness, leading to high variation in tablet hardness. Conversely, the press can be set to make the compression roller move up at each compression. In this arrangement, all tablets are compressed at the same peak force, providing a much reduced variation in tablet hardness. The tablet press is

equipped with a linear variable displacement transducer sensor that measures compression-roller movement accurately. A heavy tablet causes the compression roller to move more, and a light tablet causes less movement. This provides a tablet weight control method, called "tablet weight control by displacement," with a linear relationship between tablet weight and displacement. Accordingly, more accurate tablet weight for smaller tablets than the conventional tablet weight control by force is assured.

Floating compression rollers also provide an effective means to increase dwell at high turret revolutions. Increasing the dwell time at pre- and main compression and at high turret speed is necessary to improve deaeration and uniform distribution of compaction stress in the die prior to final compaction at high tablet output. This provides reduced risk of capping, better bonding of layers, in the case of bilayer tablets, and improved tablet tensile strength. When compressed to equal force, variations in tablet weight do not affect tensile strength. Therefore, tablets maintain a consistent clinical efficacy. Equal force tableting is also of interest when compacting coated pellets or when producing of Orally Disintegrating Tablets.

Operation of Rotary Machines

Before inserting punches and dies, make certain the pressure has been released from the pressure wheel. The die holes should be cleaned thoroughly, making certain 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 locks crew progressively and securely. As each screw is tightened, the die is checked to see it does not project above the die table. Insert the lower punches through the hole made available, by removing the punch head. Turn the machine by hand until the punch bore coincides with the plug hole. Insert each lower punch in its place progressively. Insert the upper punches by dropping them into place in the head. Each punch (upper and lower) should be coated with a thin film of mineral oil before insertion into the machine. Adjust the ejection cam, so 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 the machine over by hand. Increase the pressure by rotating the pressure wheel until a tablet is formed. Check the weight of the tablet, and adjust the fill to provide the desired tablet weight. Most likely, more than one adjustment of the fill will be necessary before obtaining the acceptable weight. When the fill is decreased, the pressure must be decreased to provide the same hardness in the tablet. Conversely, when the fill is increased, the pressure must be increased to obtain comparable hardness. Fill the hopper with the granulation and turn on the power. Check tablet weight and hardness immediately after the mechanical operation begins, and make suitable adjustments, if necessary.

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

oil before storing.

Other tablet machines are as follows:

1. High-Speed rotary Tablet machines
2. Multilayer rotary Tablet machines

DEFECTS IN TABLET COATING:

- **Picking and Sticking:**
  This occurs when tablets sticks to each other or to the top of the pan during drying. After drying, the point of contact remains stick to the pan or another tablet and gets detached from tablet core.
  Cause:
  Picking occurs when there is over wetting of tablets by the polymer solution, making the film become tacky which results to the tablet sticking to one another.
  Remedy:
  Over wetting can be avoided by increasing the efficiency of the drying process e.g. by increasing the air inlet temperature. Alternatively, the rate of applying coating solution can be decreased, or the solution viscosity increased.

- **Bridging:**
  This occurs when the coating fills in the lettering or logo(monogram) on the tablet and typically caused by excess application of the solution, poor design of the tablet embossing, typically high coating viscosity, high percentage of the solids in the solution, or improper atomization pressure.
  Remedy:
  Increase plasticizer content or by changing plasticizer, controlling spray rate and atomization pressure.

- **Erosion:**
  This can be result of the soft tablets, an over-wetted tablet surface, inadequate drying or lack of tablet surface strength.

- **Blistering:**
  Blistering of a surface film occurs when its elasticity or adhesive properties compromised. The result is that the film becomes detached from the tablet's surface
  Cause
  Blistering is usually a result of high temperatures that may occurs during the process, during the spraying stage or at the end of the coating process. Rapid evaporation of the solvent from core is also a reason for blistering.
  Remedy
  Use mild drying conditions
  Ensure moderate temperatures at other side of coating process

- **Chipping**
  Chipping occurs when the film becomes dented and chipped and this is most notably visible

on the edges of the tablet.

Cause

Decrease in rotational speed of the machinery during coating process.

Poor polymer coating solution: incorrect amount of plasticizer used in coating solution

Remedy

Increase hardness by increasing of film by adjusting the proportion of the plasticizer in coating solution or selecting polymer with a high molecular weight.

- **Blooming/ Hazing/ Dull film**

Blooming is a fading or dulling of a tablet color immediately or a after a prolonged period of storage at a high temperature.

Cause

Cellulosic polymer used in formulation.

Low molecular weight substances (mainly plasticizer) get collected on surface cause the dullness of the color.

Remedy

Use proper temperature during processing and storage.

Decreasing the concentration of the plasticizer can reduce the consequence of the blooming.

- **Orange peel (Roughness)**

The tablet has the appearance of an "Orange peel" (rough surface), which may also have a matt rather than glossy texture.

Cause

Poor tablet composition causing it to become soft.

It also caused by too high a spray pressure combined with a fast spray rate, leading to uneven coating. It may occur due to rapid drying or by high solution viscosity.

Remedy

Use mild drying

Use additional solvents to decrease the viscosity of the polymer solution so that spraying rate can be reduced.

- **Cracking (Splitting)**

Cracking occurs when the film coating the tablet cracks in the crown area or splits around the edges.

Cause

Cracking occurs when the film's internal stress exceeds the tensile strength of the film. This is common with higher molecular polymers or polymeric blends.

Remedy

Use lower molecular weight polymers or polymeric blends.

Also adjust plasticizer type and concentration.

- **Color variation**

Variation in the color of the tablets within a batch.

Cause

Color variations may occur by number of the different faults in preparations like poor mixing, uneven spray patterns of the machinery, insufficient coating, migration of soluble dyes-

plasticizer and other additives during drying.

Remedy

Aim for even geometric mixing, reformulate with different plasticizer and additives and/ or use mild drying conditions.

TABLET TESTING (EVALUATION OF TABLETS)

Tablet Hardness or Crushing Strength

The resistance of the tablet to chipping, abrasion, or breakage under conditions of storage, transportation, and handling, before usage, depends on its hardness. In the past, a rule of thumb described a tablet to be of proper hardness if it was film enough to break with a sharp snap, when it was held between the second and third fingers and using the thumb as the fulcrum, yet didn't break when it fell on the floor. For obvious reasons and control purposes, a number of attempts have been made to quantitate the degree of hardness. A small and portable hardness tester was manufactured and introduced in the mid-1930s by Monsanto. It now is distributed by the Stokes Div (Pennwalt) and may be designated as either the Monsanto or Stokes hardness tester.

The instrument measures the force required to break the tablet, when the force generated by a coil spring is applied diametrically to the tablet. The force is measured in kilograms. The StrongCobb 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. 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 expressed in either kilograms or pounds of force. Currently, the most widely used apparatuses to measure tablet hardness or crushing strength are the electrically operated equipment, which eliminates the operator variability. Newer equipment are also available with printers. Manufacturers, such as SOTAX,Key, Van Kel, Erweka, Dr. Schleuniger Pharmatron, and others, make electrically driven hardness testers (Fig. 27).

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

Figure-27. Electric Tablet Hardness Tester.

Tablet Thickness

The thickness of the tablet from production-run to production-run is controlled carefully. 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 ensure that every production lot will be usable with selected packaging components.

Friability

A tablet property related to hardness is friability, and the measurement is made by use of the Roche friabilator. Rather than a measure of the force required to crush a tablet, the instrument is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling, and shipping.

A number of tablets are weighed and placed in the tumbling apparatus, where they are exposed to rolling and repeated shocks, resulting from free-falls 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-28). The friability test is now included in the USP. A similar approach is taken by many manufacturers, when they evaluate a new product in the new market package, by sending the package to distant points and back, using various methods of transportation. This is called a "shipping test." The condition of the product on its return indicates its ability to withstand transportation handling.

Figure-28. Tablet Friability Testers.

<u>Uniformity of content of active ingredient:</u>

A fundamental quality attribute for all pharmaceutical preparations is the requirement for a constant dose of drug between individual tablets. In practice, small variations between individual preparations are accepted and the limits for this variation are defined as standards in pharmacopoeias.

For tablets, uniformity of dose or dose variation is tested in two separate tests: uniformity of weight and uniformity of active ingredient. These either reflect indirectly or measure directly the amount of drug substance in the tablet.

The test for uniformity of weight is carried out by collecting a sample of tablets, normally 20, from a batch and determining their individual weights.
The average weight of the tablets is then calculated. The sample complies with the standard if the individual weights do not deviate from the mean more than is permitted in terms of percentage.

Disintegration:

As discussed above, the drug release process from immediate-release tablets often includes a step at which the tablet disintegrates into smaller fragments.
In order to assess this, disintegration test methods have been developed and examples are described as official standards in pharmacopoeias.
The test is carried out by agitating a given number of tablets in an aqueous medium at a defined temperature, and the time to reach the end-point of the test is recorded. The preparation complies with the test if the time to reach this end-point is below a given limit. The end-point of the test is the point at which all visible parts of the tablets have been eliminated from a set of tubes in which the tablets have been held during agitation. The tubes are closed at the lower end by a screen and the tablet fragments formed during the disintegration are eliminated from the tubes by passing the screen openings, i.e. disintegration is considered to be achieved when no tablet fragments remain on the screen (fragments of coating may remain).

A disintegration apparatus (Fig. 29) consists normally of six chambers, i.e. tubes open at the upper end and closed by a screen at the lower. Before disintegration testing, one tablet is placed in each tube and normally a plastic disc is placed upon it. The tubes are placed in a water bath and raised and lowered at a constant frequency in the water in such a way that at the highest position of the tubes, the screen remains below the surface of the water. Tests for disintegration do not normally seek to establish a correlation with in vivo behavior. Thus, compliance with the specification is no guarantee of an acceptable release and uptake of the drug in vivo and hence an acceptable clinical effect. However, it is reasonable that a preparation that fails to comply with the test is unlikely to be efficacious. Disintegration tests are, however, useful as a means to assess the potential importance of formulation and process variables on the biopharmaceutical properties of the tablet, and a control procedure to evaluate the quality reproducibility of the tablet during production.

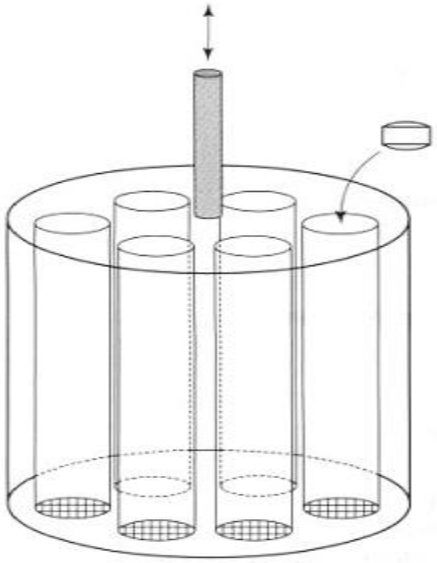


Fig. 29 Diagram of a disintegration instrument for the testing of tablet disintegration time.

Dissolution:

Dissolution testing is the most important way to study, under in vitro conditions, the release of a drug from a solid dosage form, and thus represents an important tool to assess factors that affect the bioavailability of a drug from a solid preparation. During a dissolution test the cumulative amount of drug that passes into solution is studied as a function of time. The test thus describes the overall rate of all the processes involved in the release of the drug into a bioavailable form.

Dissolution studies are carried out for several reasons:
• To evaluate the potential effect of formulation and process variables on the bioavailability of a drug;
• To ensure that preparations comply with product specifications;
• To indicate the performance of the preparation under in vivo conditions.

This last point requires that in vitro dissolution data correlate with the in vivo performance of the dosage form, which must be experimentally verified. The term in vitro/in vivo correlation in this context is related to the correlation between in vitro dissolution and the release or uptake of the drug in vivo. The establishment of such a correlation is one of the most important aspects of a dissolution test for a preparation under formulation development.

Dissolution is accomplished by locating the tablet in a chamber containing a flowing dissolution medium. So that the method is reproducible, all factors that can affect the dissolution process must be standardized. This includes factors that affect the solubility of the substance (i.e. the composition and temperature of the dissolution medium) and others that affect the dissolution process (such as the concentration of dissolved substance in, and the flow conditions of, the fluid in the dissolution chamber).
Normally, the concentration of the drug substance in the bulk of the dissolution medium shall not exceed 10% of the solubility of the drug, i.e. sink conditions. Under sink conditions, the concentration gradient between the diffusion layer surrounding the solid phase and the

concentration in the bulk of the dissolution medium is often assumed to be constant.

A number of official and unofficial methods exist for dissolution testing, which can be applied to both drug substances and formulated preparations. With respect to preparations, the main test methods are based on forced convection of the dissolution medium and can be classified into two groups: stirred-vessel methods and continuous-flow methods.

Stirred-vessel methods

The most important stirred-vessel methods are the paddle method (Fig. 30) and the rotating-basket method (Fig.31). Details of these can be found in official monographs in the European or US Pharmacopoeias. Both use the same type of vessel, which is filled with a dissolution medium of controlled volume and temperature. In the paddle method, the tablet is placed in the vessel and the dissolution medium is agitated by a rotating paddle. In the rotating-basket method, the tablet is placed in a small basket formed from a screen. This is then immersed in the dissolution medium and rotated at a given speed.

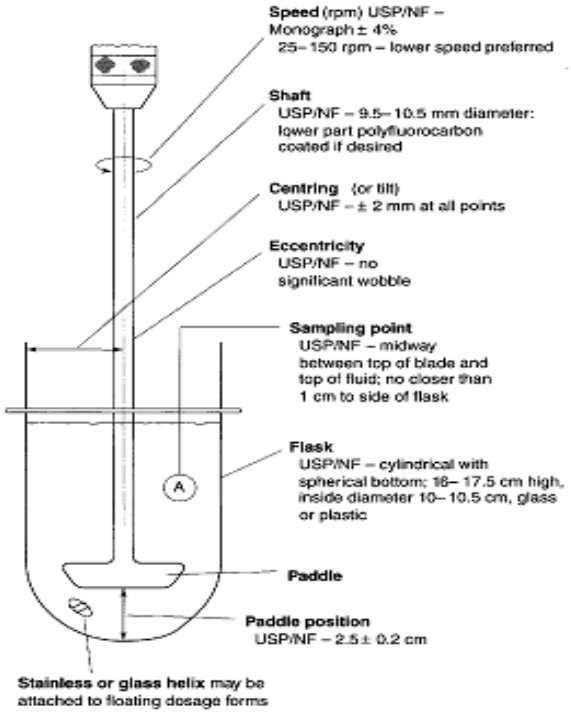


Fig. 30 Diagram of a dissolution instrument based on the rotating paddle method

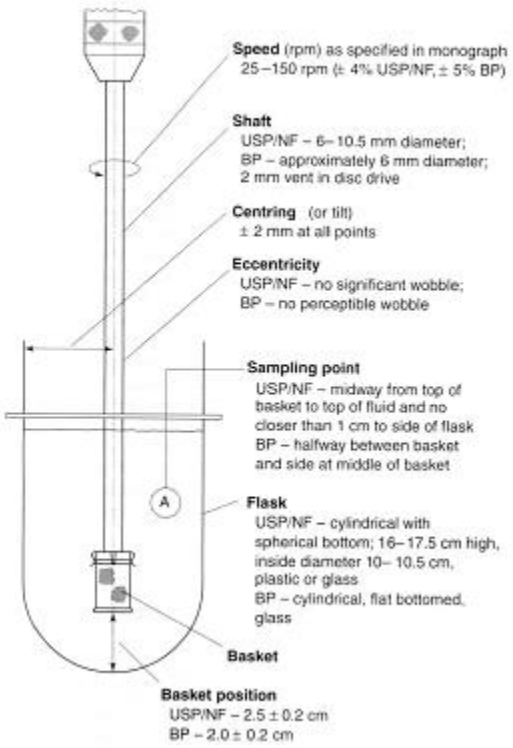


Fig. 31 Diagram of a dissolution instrument based on the rotating-basket method

Continuous-flow methods

In the continuous-flow method the preparation is held within a flow cell, through which the dissolution medium is pumped at a controlled rate from a large reservoir. The liquid which has passed the flow cell is collected for analysis of drug content. The continuous-flow cell method may have advantages over stirred-vessel methods, e.g. it maintains sink conditions throughout the experiment and avoids floating of the preparation.

The amount of drug dissolved is normally analysed more or less continuously as the concentration in the vessel at a series of consecutive times. However, sometimes a single measurement can be performed if required in the Pharmacopoeia or product specification, i.e. the amount of drug dissolved within a certain time period is determined.

The composition of the dissolution medium might vary between different test situations. Pure water may be used, but in many cases a medium that shows a closer resemblance to some physiological fluid is used. In such media the pH and ionic strength can be controlled, and surface-active agents might be added to affect the surface tension of the liquid and the solubility of the drug. Such fluids are often referred to as simulated gastric or intestinal fluids. Also, other dissolution media might be used, such as solvent mixtures, if the solubility of the drug is very low.