



Tablet manufacturing process and defects of tablets

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ABSTRACT

Tablet is defined as solid pharmaceutical dosage form containing drug substance generally with suitable diluents and prepared by either compression or molding methods. Tablets remain popular as a dosage form because of the advantages afforded, both to the manufacturer (e.g. simplicity and economy of the preparation, stability, and convenience in packing, shipping and dispensing) and the patient. Because of their composition, method of manufacture or intended use, tablets present a variety of characteristics and consequently there are several categories of tablets. Tablet formulation and design may be described as the process where by the formulator ensures that the correct amount of the drug in the right form is delivered at or over the proper time at the proper rate and in the desired location, while having its chemical integrity protected to that point. Latest concepts and regulations focus on bioavailability, bioequivalence and validation etc. impact formulation designing and manufacture.

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Introduction

The oral route of drug administration is the most important method of drug administration for systemic effects. The Parenteral route of administration is important in treating the medical emergencies in which subject is comatose or can not swallow and in providing various types of maintenance therapy. Nevertheless, about 90% of all the drugs used to produce systemic effects are administered by the oral route. Among the drugs that are administered orally, solid dosage form represents the preferred class of product. Solid dosage form provides best protection to the drug against temperature, humidity, oxygen, light and stress during transportation and also ensures accuracy of dosage, compactness, portability, blandness of taste, and ease of administration. Although the basic medicinal 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 in both production speed and the uniformity of the tablets compressed. Although tablets frequently are discoid in shape, they also exist in several shapes such as round, oval oblong, cylindrical or triangular etc. They may differ greatly in size and weight depending on the amount of the drug substance present and the intended method of administration. They are divided in to two general classes by 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.

Types of tablets

Compressed Tablets

The tablets are formed by compression of powdered, crystalline, or granular active materials (API), alone or in combination with certain excipients as required, such as binders,

disintegrants, sustained release polymers, lubricants, diluents, flavors and colorants.

A) Sugar coated tablets (sct)

B) Film coated tablets (fct)

C) Enteric-coated tablets (ect)

D) Multi compressed tablets (mct): these are compressed Tablets made by more than one compression cycle.

I) Layered tablets

ii) Press coated tablets

E) Sustained release tablets

F) Tablets for solution

G) Effervescent tablets

H) Compressed suppositories or inserts

I) Buccal and sublingual tablets

Molded tablets or tablet triturates (tt)

Tablet triturates usually are made from moist material, using a mold that gives them the shape of cut sections of cylinder. Such tablets must be completely and rapidly soluble. Suitable water-soluble lubricant is many times a constraint.

Dispensing Tablets (Dt)

These tablets provide a convenient quality of potent drug that can be incorporated readily in to powders and liquids, thus circumventing the necessity to weigh small quantities. These tablets are supplied primarily as a convenience for extemporaneous compounding and never dispensed as a dosage form.

Hypodermic Tablets (Ht)

Hypodermic tablets are soft, readily soluble tablets. Though these tablets are now made for oral administration they are not yet recognized by the official compendia.

Advantages of the tablets

The additional advantages of tablet dosages forms are as follows:

- Their cost is lowest of all the dosage forms.
- They are in general the easiest and cheapest to package and ship of all oral dosage forms.

Dispensing (weighing and measuring)

Dispensing is the first step in any pharmaceutical manufacturing process. Dispensing is one of the most critical steps in pharmaceutical manufacturing; as during this step, the weight of each ingredient in the mixture is determined according to dose. Dispensing may be done by purely manual by hand scooping from primary containers and weighing each ingredient by hand on a weigh scale, manual weighing with material lifting assistance like Vacuum transfer and Bag lifters, manual or assisted transfer with automated weighing on weigh table, manual or assisted filling of loss-in weight dispensing system, automated dispensaries with mechanical devices such as vacuum loading system and screw feed system. Issues like weighing accuracy, dust control laminar air flow booths, glove boxes), during manual handling, lot control of each ingredient, material movement into and out of dispensary should be considered during dispensing.

Sizing

The sizing (size reduction, milling, crushing, grinding, pulverization) is an important step (unit operation) involved in the tablet manufacturing. In manufacturing of compressed tablet, the mixing or blending of several solid ingredients of pharmaceuticals is easier and more uniform if the ingredients are approximately of same size. This provides a greater uniformity of dose. A fine particle size is essential in case of lubricant mixing with granules for its proper function. Advantages associated with size reduction in tablet manufacture are as follows:

- i) It increases surface area, which may enhance an active ingredient's dissolution rate and hence bioavailability.
- ii) Improved the tablet-to-tablet content uniformity by virtue of the increased number of particles per unit weight.
- iii) Controlled particle size distribution of dry granulation or mix to promote better flow of mixture in tablet machine.
- iv) Improved flow properties of raw materials.
- v) Improved colour and/or active ingredient dispersion in tablet excipients.
- vi) Uniformly sized wet granulation to promote uniform drying.

There are also certain disadvantages associated with this unit operation if not controlled properly. They are as follows:

- i) A possible change in polymorphic form of the active ingredient, rendering it less or totally inactive, or unstable.
- ii) A decrease in bulk density of active compound and/or excipients, which may cause flow problem and segregation in the mix.
- iii) An increase in surface area from size reduction may promote the adsorption of air, which may inhibit wettability of the drug to the extent that it becomes the limiting factor in dissolution rate.

A number of different types of machine may be used for the dry sizing or milling process depending on whether gentle screening or particle milling is needed. The ranges of equipment employed for this process includes Fluid energy mill, Colloidal mill, Ball mill, Hammer mill, Cutting mill, Roller mill, Conical mill, etc.

Powder blending

The successful mixing of powder is acknowledged to be more difficult unit operation because, unlike the situation with liquid, perfect homogeneity is practically unattainable. In practice, problems also arise because of the inherent cohesiveness and resistance to movement between the individual particles. The process is further complicated in many system, by the presence of substantial segregation influencing the powder mix. They arise because of difference in size, shape, and density of the component particles.

The powder/granules blending are involved at stage of pre granulation and/or post granulation stage of tablet manufacturing. Each process of mixing has optimum mixing time and so prolonged mixing may result in an undesired product. So, the optimum mixing time and mixing speed are to be evaluated. Blending step prior to compression is normally achieved in a simple tumble blender. The Blender may be a fixed blender into which the powders are charged, blended and discharged. It is now common to use a bin blender which blends. In special cases of mixing a lubricant, over mixing should be particularly monitored. The various blenders used include "V" blender, Oblicone blender, Container blender, Tumbling blender, Agitated powder blender, etc. But now a day to optimize the manufacturing process particularly in wet granulation the various improved equipments which combines several of processing steps (mixing, granulation and/or drying) are used. They are "Mixer granulator" or "High shearmixing machine".

Granulation

Following particle size reduction and blending, the formulation may be granulated, which provides homogeneity of drug distribution in blend.

Drying

Drying is a most important step in the formulation and development of pharmaceutical product. It is important to keep the residual moisture low enough to prevent product deterioration and ensure free flowing properties. The commonly used dryer includes Fluidized – bed dryer, Vacuum tray dryer, Microwave dryer, Spray dryer, Freeze dryer, Turbo – tray dryer, Pan dryer, etc.

Tablet compression

After the preparation of granules (in case of wet granulation) or sized slugs (in case of dry granulation) or mixing of ingredients (in case of direct compression), they are compressed to get final product. The compression is done either by single punch machine (stamping press) or by multi station machine (rotary press). The tablet press is a high-speed mechanical device. It 'squeezes' the ingredients into the required tablet shape with extreme precision. It can make the tablet in many shapes, although they are usually round or oval. Also, it can press the name of the manufacturer or the product into the top of the tablet. Each tablet is made by pressing the granules inside a die, made up of hardened steel. The die is a disc shape with a hole cut through its centre. The powder is compressed in the centre of the die by two hardened steel punches that fit into the top and bottom of the die.

The punches and dies are fixed to a turret that spins round. As it spins, the punches are driven together by two fixed cams - an upper cam and lower cam. The top of the upper punch (the punch head) sits on the upper cam edge. The bottom of the lower punch sits on the lower cam edge. The shapes of the two cams determine the sequence of movements of the two punches. This sequence is repeated over and over because the turret is spinning round.

The force exerted on the ingredients in the dies is very carefully controlled. This ensures that each tablet is perfectly formed. Because of the high speeds, they need very sophisticated lubrication systems. The lubricating oil is recycled and filtered to ensure a continuous supply.

Common stages occurring during compression

Stage1: Top punch is withdrawn from the die by the upper cam
Bottom punch is low in the die so powder falls in through the hole and fills the die

Stage2: Bottom punch moves up to adjust the powder weight-it raises and expels some powder

Stage 3: Top punch is driven into the die by upper cam Bottom punch is raised by lower cam Both punch heads pass between heavy rollers to compress the powder

Stage 4: Top punch is withdraw by the upper cam Lower punch is pushed up and expels the tablet Tablet is removed from the die surface by surface plate

Stage 5: Return to stage 1

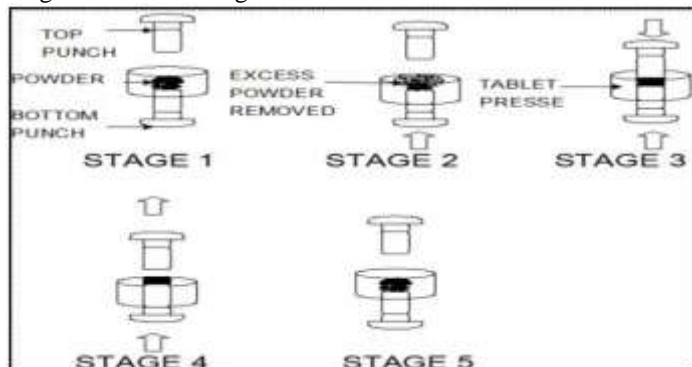


Figure.3 . Stage Occurring During Compression

Auxiliary Equipments

I. Granulation Feeding Device:

In many cases, speed of die table is such that the time of die under feed frame is too short to allow adequate or consistent gravity filling of die with granules, resulting in weight variation and content uniformity. These also seen with poorly flowing granules. To avoid these problems, mechanized feeder can employ to force granules into die cavity.

II. Tablet weight monitoring devices:-

High rate of tablet output with modern press requires continuous tablet weight monitoring with electronic monitoring devices like Thomas Tablet Sentinel, Pharmakontroll and Killan control System-MC. They monitors force at each compression station by strain gage technology which is then correlated with tablet weight.

III. Tablet Deduster:

In almost all cases, tablets coming out of a tablet machine bear excess powder on its surface and are run through the tablet deduster to remove that excess powder.

IV. Fette machine

Fette machine is device that chills the compression components to allow the compression of low melting point substance such as waxes and thereby making it possible to compress product with low melting points.

Packaging

Pharmaceutical manufacturers have to pack their medicines before they can be sent out for distribution. The type of packaging will depend on the formulation of the medicine. 'Blister packs' are a common form of packaging used for a wide variety of products. They are safe and easy to use and they allow the consumer to see the contents without opening the pack. Many pharmaceutical companies use a standard size of blister pack. This saves the cost of different tools and to change the production machinery between products. Sometimes the pack may be perforated so that individual tablets can be detached. This means that the expiry date and the name of the product have to be printed on each part of the package. The blister pack itself must remain absolutely flat as it travels through the packaging processes, especially when it is inserted into a carton. This poses interesting problems for the designers. Extra ribs are added to the blister pack to improve its stiffness.

Recent advances in tablet formulation technology

The recent trends in tablet formulation are

1. Versatile immediate release tablet systems including fast dissolving drug delivery systems, orally disintegrating tablets/orally dispersible tablets, orally dispersible mini tablets, mouth dissolving/ fast dissolving tablets, novel fixed dose combination tablet ACCU-BREAK technology (inactive layer between two different drug layers), conventional effervescent, uncoated and film-coated tablets etc.

2. Modified release tablet formulations including ring cap coated tablet ALZA, layered tablets (in lay, tablet in tablet, bilayered tablet), novel chewable sustained release tablet and direct compression medicated chewing gum.

3. Excipient technology is advancing to produce directly compressible materials for both immediate release as in mouth dissolving systems, or for sustained release systems. The research in excipients is meeting pace with the high throughput production of tablets. Research is also advancing into obtaining excipients from natural sources. Various commercial excipients such as Lycoat, Readily coat, Instamodel and Instanute DR are available in the market.

Patented Technologies For Fast Dissolving Tablets

Zydis Technology

Zydis, the best known of the fast-dissolving/disintegrating tablet preparations was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue. A Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatin. The product is very lightweight and fragile, and must be dispensed in a special blister pack. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds. The Zydis formulation is also self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth.

Durasolv Technology

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packed into conventional packaging system like blisters. Durasolv is an appropriate technology for products requiring low amounts of active ingredients.

Orasolv Technology

Orasolv Technology has been developed by CIMA labs. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable and packaged in specially designed pick and place system.

Flash Dose Technology

Flash dose technology has been patented by Fuisz. Nurofen meltlet, a new form of ibuprofen as melt-in-mouth tablets, prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consists of self binding shearform matrix termed as "floss". Shearform matrices are prepared by flash heat processing.

Wowtab Technology

Wowtab Technology is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water ". In this process, combination of low mouldability saccharides and high

mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide and granulated with a high mouldability saccharide and compressed into tablet.

Flashtab Technology

Prographarm laboratories have patented the Flashtab technology. Tablets prepared by this system consist of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation, and extrusion spherulisation. All the processing utilized conventional tableting technology.

Marketed scope in tablet compression technology

The market for tablet compression technology and the demands placed on equipment manufacturers have changed quite significantly in recent years. This has been driven by a number of factors. Firstly, the pharmaceutical industry has seen a significant shift of investments in solid dosage production equipment towards generics and contract manufacturing. As the companies in this segment of the market are, by nature, strongly focused on cost reduction, a big emphasis is placed on productivity, flexibility and process yield (i.e., minimal product loss). Equipment cost and reliability, as well as fast on-site assistance have also become key selection criteria. research and development based companies have also been forced to follow this cost reduction trend. Secondly, the meteoric growth of new pharmaceutical markets in the Middle East and the Far East (e.g., India, China, South Korea) has led investments in solid dosage equipment in these regions to surpass the investments made in North America and Europe. This puts an increased pressure on equipment price and has resulted in several Western based companies moving the design, manufacture and assembly of their equipment to Asia.

Mottling

Unequal distribution of colour on the tablet surface with light and dark areas standing out in an otherwise uniform coloured surface

Cause :

- Variation in the colours of ingredients (drug and other additives)
- Drugs with degradation nature and have different coloured degraded products
- Migration of dye to the surface of granulation during drying. At high temperature dyes are easily migrate to surface and spread to upper surface.
- Uneven distribution of colored adhesive gel solutions resulting in precipitation
- The improper size either large or small particles enhances color distribution. During preparation dyes are not properly mixed and not selected ideally or any incompatibility will tends to enhance appearance of color on tablet surface.
- Improper storage conditions.

Remedy:

- By using bright coloring agent that will mask all the color variations of the ingredients
- Proper drying by reducing the drying temperature
- Colored adhesive gel solutions must be added when they are hot too much cooler powder mixtures to avoid precipitation
- It is better to incorporate fine powder adhesives like acacia and tragacanth into product before adding the granulating fluid
- By changing the solvent system or binder system
- Grinding to small particle size

Special Problem in Compressing Tablet Process

Capping And Laminating

Capping :

Capping Continuously high speed of tablet machine and high degree of compression setting makes tablet to separate main surface into individual surface. Avoid defective punches and dies. High temperature adjustment also favor capping. Distance between upper and lower punches will entrap air is bone factor for capping. Fine particles were susceptible than coarse particles will affect ideality of tablets. Capping minimized by keeping the feed material with cohesive nature.

Lamination :

Lamination It is major problem among of all defects. Occur upon storage period, or soon after compression. Air entrapment between layers of tablet. Low levels of binding agent. It minimized by improving lubricant concentration. Change the method of granulation. By direct compression technique it is prevented to some extent. Use always dry material (feed).

Table-2

Causes	Remedy
Air entrapment in the tablet among granules or among particles	By pre-compression, Reducing final compression, Minimizing tableting rate
Deformational properties of formulation during and after compression	Increasing stress relaxation time
Improper/Deep concave punches	Better to use flat punches
Over dried granules (Due to lack of cohesion)	By maintaining moisture levels using hygroscopic materials like MC (Methyl Cellulose), Sorbitol, PEG 4000 (Polyethylene glycol) etc.
Improper tooling: • Concave edges of punches turning claw shaped • Greater radius of curvature of punch face • Dies developing a wear ring shape • Improper adjustment of sweep off blade • Less rise of lower punch during ejection of table	Proper tooling: • Checking of punches and replacing them • Proper checking and replacing them • Turning the die over so that compression occurs in an unworn area above ring • Proper setting of sweep off blade & lower punch rise
Poor compressibility observed during direct compression technique	Relative compressibility is to be maintained

Picking

Adherence of the tablet material from the surface of a tablet by a punch.

Causes:

Because of engraving or embossing or debossing on the punch tips like small enclosed areas in the letters like "A", "B", "D", "O", "Q" etc

Remedy:

- Lettering should be designed as large as possible, even the tablet size can be increased by reformulation
- Colloidal silica can be added as polishing agent to formula
- Using additional binder to increase cohesiveness of granules and thereby causing decreased adherence
- Plating of punch faces with a chromium material to obtain smooth face which is non-adherent
- Avoid wet granules.

Sticking

Sticking always occurs in low melting point substances, and moisture supports this defects, lower the speed up of upper and lower punch leads to weight variation of tablets. It produces rough and chipping surface tablets. It develops material on both punches. Lack of drying is basis of this one.

Causes:

- Presence of low melting point substances in the formula ex. Stearic acid, PEG (Polyethylene glycol) etc , which gets soften due to compressive heat
- Excessive moisture in the granules

Remedy:

- Partial or complete substitution of low melting point components with high melting point materials in the formula
- Proper drying of the granules to remove excessive moisture
- Selection of Binding agent is essential to solve sticking.
- Ideal selection of lubricant in desired proportion will minimized this problem.

Weight Variation (Granule size and size distribution)**Causes:**

- Improper blending of granules
- Lack of sufficient of lubricant
- Abnormal uniform mixing of all excipients.
- Improper tool setting of machine. Hi-speed running of machine.
- improper glidant selection.
- Improper drying making tablet with different weight.
- Proportion of small to large granules influence the die filling capacity and thereby results in weight variation of tablets
- If large granules are used to fill small die cavities, even a small difference in granules results in high percent weight variation of tablets

Remedies:

- Uniform size distribution (Narrow) and smaller granular size is preferable

POOR FLOW**Causes:**

- Improper design of hopper
- Poor flow of granules
- Bridging/arching and rat-holing of granules at the bottom of the hopper
- Segregation or stratification of particles due to use of flow promoting devices like vibrators
- Surges of excessive flow above the hopper

Remedies:

- Flow can be improved by using glidants like talc, colloidal silica etc.
- By proper design of the hopper
- By using flow enhancing devices like vibrators
- By preparing uniform sized and shaped granules

Poor Mixing**Causes:**

- Improper mixing of ingredients like glidants and lubricants useful for proper flow and punching
- Insufficient or inadequate time of mixing

Remedy:

- Proper mixing by maintaining adequate time and using suitable mixer

Punch Variation**Cause:**

- Unequal lengths of lower punches which results in variations of granular volume filled in die

Remedy:

- Proper tooling by using good and uniform sized punches

Hardness Variation**Causes:**

- Due to weight variation in granules filled in die
- Space between lower and upper punches

Remedy:

- Proper tooling of machine

Double Impression**Cause:**

Uncontrolled movement of punches with engravings on them

Remedy:

Using anti-turning devices

Chipped edge :

Tablets having sharp edge, elongated tablets are prone to chipped edge. Granules are subject to high temperature will improve chipped surface (high drying). This defects accompanied with damaged surfaces at its corners of tablet ,easily fragmented by even smooth handling also. Due to rough handling. Tablet shape is abnormal than normal. Use optimum level of binding agent.

Print defect :

It is mainly observed in tablets which having hard corners/designs on punches. It takes due to improver punch cycle. Punches having rough surface . Improper blending of total powder. Letter are designed with uneven surfaces on punches.

HAIR/FIBRE :

HAIR/FIBRE As name itself indicates some unwanted particles/hair are appeared on tablet surface. Not following SOP. Operator not implementing cGMP. Lack of attention of operator. Punches are cleaned before installing in their respective places. Lack of cleaning/spacious rooms.

Black SPOT/STAIN :

Stains or spots will be appear on tablet surface. Migration of coloring agent upon storage. High temperature is key factor for penetration of dye into upper surface. Improper cleaning of punches. Mainly observed in colored tablets. Observe in high concentration of dyes. Incompatibility among excipients and API

Soft Tablets :

The tablets are susceptible to hydrolysis will develop soft nature. Improper storage. Mainly observed in polymer/coated tablets. Lack of drying will enhance the softness. Granulation particles will completely free from moisture by keeping to drying condition properly. Soft tablet will form initiate/basis for sticking or picking defects. Use of lubricant that impart waxy nature. Application of low compaction pressure. The strength of bond is weakened across granules.

Protracted disintegration :

Disintegration time is extended in tablet. Use of high compression on punches. Incorporation of lubricant in excess quantity. Overcome by using proper suitable surfactant concentration. Addition of more concentration of binding agent. Too low compression also favors extend disintegration time.

Conclusion

Among the different routes of drug administration, oral route is mostly preferred. About 90% of drugs are administered orally for systemic effect. Various kinds of solid dosage forms like tablet, capsules, pills, syrups etc are administered through oral route of drug administration. In orally administered dosage forms, tablet represents the preferred choice of class of product. The tablet is convenient, in terms of self medication, ease of administration, compactness, accurate dose, avoidance pain, versatility and most importantly patient compliance.

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