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Improved Tablet Production by Modified Granulation Techniques - A Review

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Abstract

Tablets are one of the oral solid dosage forms most widely used by the pharmaceutical manufacturers, physicians and patients due to the convenience in manufacturing, administration and suitability for delivery of most of the active ingredients. Tablets are manufactured by different methods such as wet granulation, dry granulation and direct compression. Granulation is defined as the size enlargement process in which fine and smaller particles are aggregated to form strong and stable particles called granules. Present article mainly focuses on advanced granulation techniques such as moisture activated dry granulation, thermal adhesion granulation, foam binder granulation etc.

Keywords: Tablets, Granulation, Direct compression, Moisture activated dry granulation, Foam binder granulation.

Contents

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1. Introduction

Tablet is a unit solid dosage form containing active ingredient with or without the suitable excipients. These are the most widely used dosage form by the pharmaceutical manufacturers, physicians and patients. The main objective of the design and manufacture of the compressed tablet is to deliver orally the correct amount of drug in the proper form, at or over the proper time and in desired location, and to have its chemical integrity protected at the point of its action. The physical design, manufacturing process, and complete chemical makeup of the tablet can have a profound effect on the efficiency of the drug being administered [1].

Tablet Manufacturing Process:

Tablet manufacturing process can be broadly classified as granulation and direct compression. Granulation process may be defined as the size enlargement process in which fine or coarse particles are converted into physically stronger and larger agglomerates having good flow properties, better compression characteristics and uniformity and

a process for collecting particles together by creating bonds between them. It is the most widely used technique in the pharmaceutical industry for the preparation of materials for tableting [2]. Granulation may be either wet granulation i.e., by using binder solution or dry granulation i.e., by using dry binder. Pharmaceutical granules typically have a size range between 0.2 and 4.0 mm, depending on their subsequent use. The most popular, which is used by over 70% of formulation in tablet manufacturing is wet granulation.

[A] Wet granulation

It is the most widely used agglomeration process in the pharmaceutical industry. This process involves the mixing of the powder with the granulating liquid, wet sizing and drying [3-7].

a. Important steps involved in the wet granulation
b. Mixing of the drug(s) and excipients
c. Preparation of binder solution
d. Mixing of binder solution with powder mixture to form wet mass.
e. Drying of moist granules
f. Mixing of screened granules with disintegrant, glidant, and lubricant.

Advantages:

a. Permits mechanical handling of powders without loss of quality of blend.
b. The flow properties of powder are improved by increasing particle size and sphericity.
c. Increases and improves the uniformity of powder density.
d. Improves cohesion during and after compaction.
e. Air entrapment is reduced.
f. Reduces the level of dust and cross contamination.
g. Allows for the addition of a liquid phase to powders.
h. The hydrophobic surfaces are made hydrophilic.

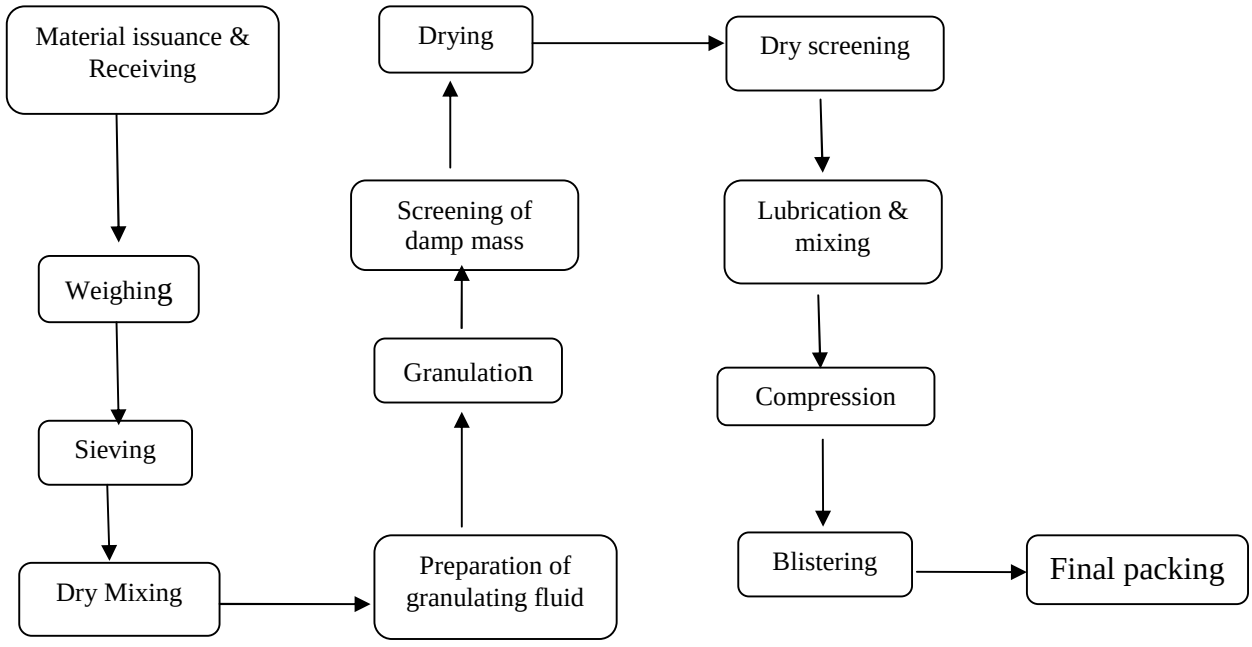


Figure 1: Flow chart for wet granulation process

Limitation of wet granulation

a. The greatest disadvantage of wet granulation is its cost. It is an expensive process because of labor, time, equipment, energy and space requirements.
b. Loss of material during various stages of processing.
c. Stability may be major concern for moisture sensitive or thermo labile drugs.
d. Multiple processing steps add complexity and make validation and control difficult.
e. An inherent limitation of wet granulation is that any incompatibility between formulation components is aggravated.

[B] Dry granulation:

In dry granulation process the compression of the powder is without the use of heat and solvent. It is the most desirable of all methods of granulation. The two basic steps are the formation of compact of material by compression and then to mill the compact to obtain the granules. Two methods are used for dry granulation. The

most widely used method is slugging in which powder is recompressed and resulting tablet or slugs are milled to obtain the granules. The other method is to precompress the powder with pressure rolls using a machine such as chilsonator [3-7].

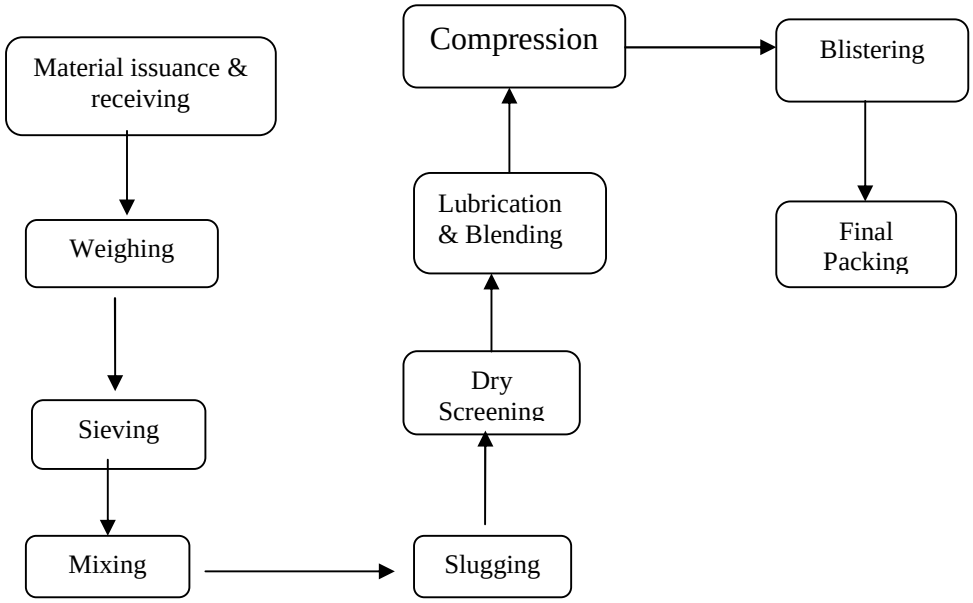


Figure 2: Flow chart for dry granulation process

Roller Compaction:

The compaction of powder by use of pressure roll can also be accomplished by a machine called chilsonator. Unlike tablet machine, the chilsonator turns out a compacted mass in a steady continuous flow. The powder is fed down between the rollers from the hopper which contains a spiral auger to feed the powder into the compaction zone. Like slugs, the aggregates are screened or milled to produce granules.

Use: Used in the production of directly compressible excipients, the compaction of drugs and drug formulations, the granulation of inorganic materials, the granulation of dry herbal material and the production of immediate/sustained release formulations.

Processing steps:

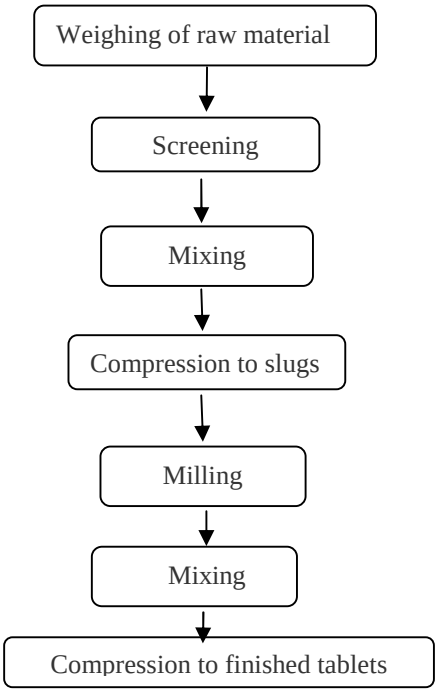


Figure 3: Flow chart for roller compaction process

Advantages:

The main advantages of dry granulation or slugging are that it uses less equipments and space. It eliminates the need for binder solution, heavy mixing equipment and the costly and time consuming drying step required for wet granulation. Slugging can be used for advantages in the following situations:

a. For moisture sensitive material
b. For heat sensitive material
c. For improved disintegration since powder particles are not bonded together by a binder.

Disadvantages:

a. It requires a specialized heavy duty tablet press to form slug.
b. It does not permit uniform colour distribution as can be achieved with wet granulation where the dye can be incorporated into binder liquid.
c. The process tends to create more dust than wet granulation, increasing the potential contamination.

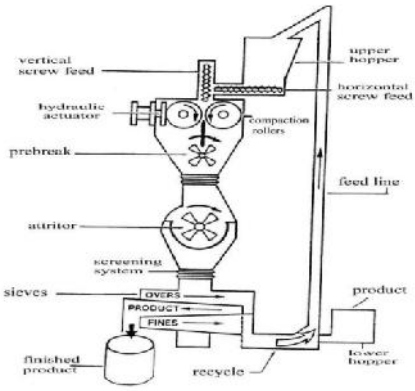


Figure 4: Chilsonator

[C] The direct compression process

This method is used when a group of ingredients can be blended and placed in a tablet press to make a tablet without any of the ingredients having to be changed. This is not very common because many tablets have active pharmaceutical ingredients which will not allow for direct compression due to their concentration or the excipients used in formulation are not contributory to direct compression [3-7].

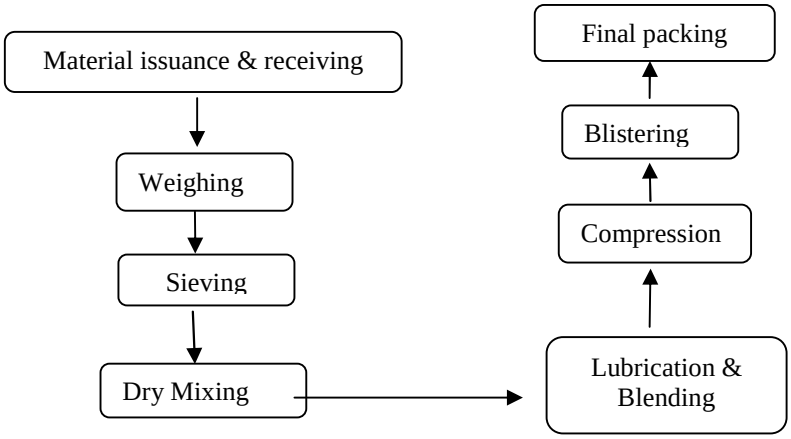


Figure 5: Flow chart for Direct compression process

Advantages of Direct Compression:

1. Cost Effectiveness

The main advantage of direct compression over wet granulation is that it is more economic since the direct compression requires few unit operations. This means less equipment, lower power consumption, less space, less time and less labor leading to reduced production cost of tablets.

2. Stability

Direct compression is more suitable for moisture and heat sensitive APIs, as it eliminates wetting and drying steps and increases the stability of active ingredients by reducing harmful effects. Changes in dissolution profiles are less likely to occur in tablets made by direct compression on storage than the tablets made from granulations. This is

most important because the official compendium now requires dissolution specifications in most solid dosage forms.

3. Faster Dissolution

Disintegration or dissolution is the rate limiting step in absorption in the case of tablets containing poorly soluble API prepared by wet granulation. The tablets prepared by direct compression disintegrate into API particles instead of granules which directly come in contact with dissolution fluid and exhibits comparatively faster dissolution.

4. Less wears & tears of punches

The high compaction pressure involved in the production of tablets by slugging or roller compaction can be avoided by adopting direct compression. The chances of wear and tear of punches and dies are less.

5. Simplified Validation

Materials are "in process" for a shorter period of time, resulting in less chance for contamination or cross contamination, and making it easier to meet the requirement of current good manufacturing practices. Due to fewer unit operations, the validation and documentation requirements are reduced. Due to the absence of water in granulation, chance of microbial growth is minimal in tablets prepared by direct compression.

2. Limitations of direct compression

1. Segregation

Direct compression is more prone to segregation due to the difference in density of the API and excipients. The dry state of the ingredients during mixing may induce static charge and lead to segregation. This may lead to the problems like weight variation and content uniformity.

2. Cost

Directly compressible excipients are the special products produced by patented spray drying, fluid bed drying, roller drying or co-crystallization. Hence, these products are relatively costly than the respective raw materials.

3. Low dilution potential

Most of the directly compressible materials can accommodate only 30-40 % of the poorly compressible active ingredients. So there is a need to produce large tablets which may create difficulty in swallowing.

4. Re-workability

All the spray-dried directly compressible adjutants show poor rework ability since on preparation of tablets the original spherical nature of the excipient particles is lost. API that has poor flow properties and/or low bulk density is difficult to process by direct compression.

5. Lubricant sensitivity

Lubricants have a more adverse effect on the filler, which exhibit almost no fracture or shear on compression (e.g. starch 1500). The softening effects as well as the hydrophobic effect of alkaline stearates can be controlled by optimizing the length of blending time to as little as 2-5 min.

6. Variation in functionality

There is a lack of awareness in some situations that the excipient behave differently, depending upon the vendor so much that substitution from one source to that of another source is not possible. Hence, there is a need for greater quality control in purchasing of raw material to assure uniformity in the batch.

Specialised Granulation Methods / Techniques

(i) Moisture activated dry granulation
(ii) Thermal adhesion granulation
(iii) Pneumatic dry granulation
(iv) Melt / thermoplastic granulation
(v) Fluidized bed granulation
(vi) Extrusion-spheronization granulation
(vii) Spray drying granulation
(viii) Freeze granulation
(ix) Foam binder granulation
(x) Steam granulation

(i) Moisture activated dry granulation (MADG):

MADG technology is widely used in granulation of moisture sensitive active pharmaceutical ingredients. This process involves the utilization of very little granulating fluid, to activate granule formation and it also eliminates the drying steps by using moisture absorbing materials like microcrystalline cellulose (MCC), potato starch, a mixture of MCC and potato starch (50% w/w), silicon dioxide, Spress® B818 Pregelatinized Corn Starch NF, Maltrin® maltodextrins, to remove excess of moisture present in the granulate. This process is accomplished by two major steps a) agglomeration and b) moisture distribution. It involves the formation of wet mass by using granulating fluid and then utilizing the moisture absorbing materials to dry the granules. In this technique small amount of water (1-4%) is added to agglomerate the powder blend containing active ingredient, binder and excipients using blender followed by addition of moisture absorbing material. The factors which influence the

overall process are impeller speed, chopper speed and time, spray rate and volume, droplet size, nozzle distance and position [8].

Advantages :

1. A simple, clean, lean process that utilizes very little granulating fluid.
2. Produce granules with more uniform particle size distribution (particle size range of 150–500 μm) and excellent flowability.
3. Economical and time efficient, as requires less energy and eliminates drying step.
4. Suitable for continuous processing.
5. Used for preparation of floating and sustained release products.

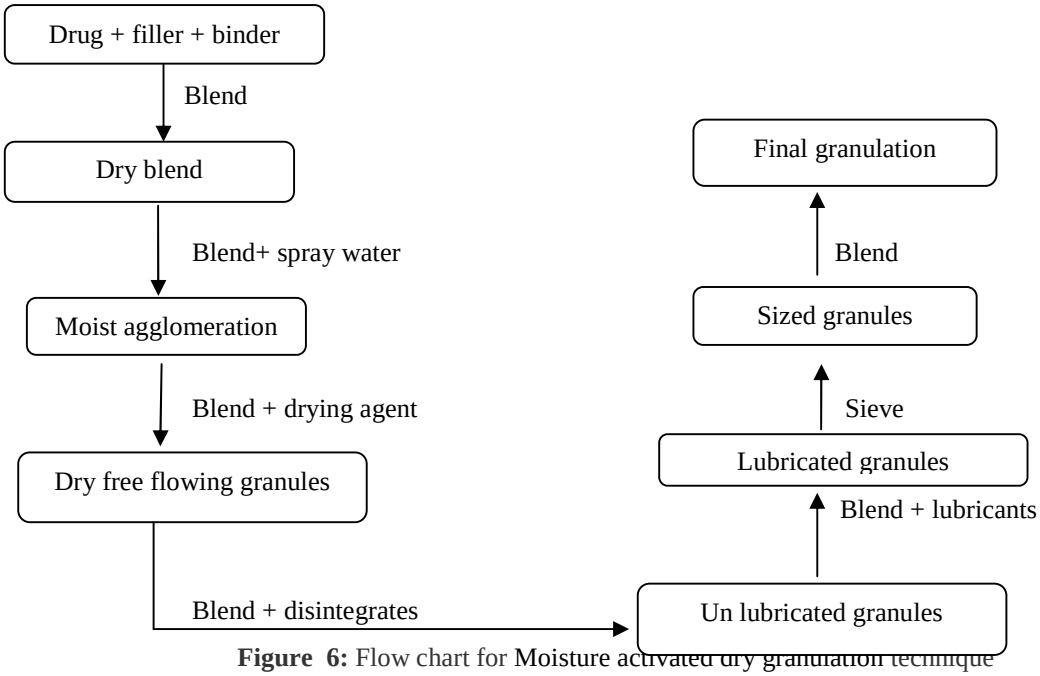


Figure 6: Flow chart for Moisture activated dry granulation technique

Disadvantages:

1. Unsuitable for thermo-labile, moisture sensitive, high moisture absorbing substances.
2. Difficult to develop formulations with high drug loading.

(ii) Thermal adhesion granulation:

It involves granulation of the blend by addition of very less amount of water or solvents. In this process the binder is first moisturized by spraying water or ethanol, and then this blend is transferred into a pre warmed glass bottle and sealed. It is then heated properly by an infrared lamp to raise surface temperature of the vessel to 90ºC-105ºC in case of water and 70ºC-90ºC in case of ethanol, and mixed under tumble rotation for 3-20 minutes until the granules are formed [9-14].

Thermal adhesion granulation process is performed under low moisture content or low content of pharmaceutically acceptable solvent by subjecting a mixture of excipients to heating. This method utilizes less water or solvent when compared to conventional wet granulation technique.

Advantages:

1. Utilizes less amount of water or solvent.
2. Granules with good flow properties and binding capacity were obtained even with substances having poor tabletting properties.
3. Minimizes the dust generation during powder processing.

(iii) Pneumatic dry granulation:

Pneumatic dry granulation is a novel granulation technique in which standard roller compaction method is used to compact materials at very low compaction force with subsequent milling and fractionating milled materials. To separate the granules and to recycle the rejected fraction, a newly innovated fractionating device is employed. Pneumatic dry granulation is suitable for automatic or semi-automatic production of granules [9-14].

Advantages:

a. Can achieve high drug loading of traditionally proven difficult materials.
b. Faster development (within weeks) even with historically proven difficult materials.
c. Decreases cost of product by minimizing waste through recycling and production cost.

d. Excellent stability with enhanced shelf-life.
e. Compatible with other technologies like coating, sustained release, fast release.
f. Suitable for thermo-labile and moisture sensitive drugs.
g. Taste masking and tailoring of release rate and time can be achieved.
h. Produce soft and porous granules with high flowability and compressibility.
i. Possesses potentiality to handle sterile products or toxic materials.
j. Lowers scale-up cost and problems.

(iv) Melt agglomeration/thermoplastic granulation:

Melt agglomeration is the technique which is used for the production of controlled release reservoir systems consisting of polyethylene vinyl acetate copolymer. In this method granulation is achieved by using a meltable binder that is in solid state at room temperature and melts in the temperature range of 50ºC-80ºC this melted binder acts as a binding liquid [9-14]. It utilizes two methods:

Spray on method: it involves spraying of the molten binder onto the powder and by simple cooling of the product at room temperature followed by milling to obtain dried granules.

Insitu melt granulation method:

It employs a solid binder which is heated above its melting point by hot air, when it is processed in fluidized bed processor. In melt agglomeration process solid fine particles are bound together into agglomerates by agitation, kneading, and layering in the presence of molten binding liquid. Dry agglomerates are obtained by cooling the molten binding liquid. During the agglomeration process, there is a gradual change in the size and shape of the agglomerates. Melt agglomeration is achieved by using equipments such as rotating drums or pans, fluid-bed granulators, low-shear mixers such as Z-blade, planetary mixers and high shear mixer granulators.

Advantage:

1. Both aqueous and non-aqueous solvent were not used.
2. Time and cost effective as involves fewer processing steps and eliminates drying step.
3. Uniform dispersion of fine particle occurs.
4. Release profile of drugs can be controlled and modified.
5. Suitable for enhancing dissolution profile and bioavailability of poorly water soluble drugs by forming solid dispersion.
6. Product exhibit good stability at varying pH and moisture levels.
7. Higher degree of regulatory compliance.

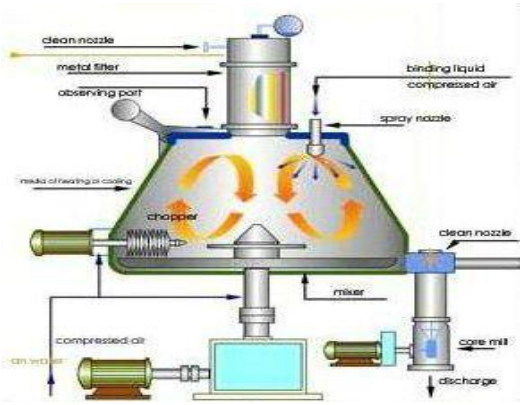


Figure 7: High shear mixer granulator

Disadvantages:

1. Thermo-labile materials were poor candidates.
2. Requires high energy input.
3. Melting or softening of the low melting point binder may occur during handling and storage of agglomerates.

(v) Fluidized bed granulation:

Fluidized bed processing is a air suspension technique in which binder solution is sprayed on to the fluidized powder bed to get finer, free flowing and homogenous granules. This fluidized bed processor contains air handling unit, product container, air distributor, spay nozzle, disengagement area, process filters, exhaust blower/fan, control system, and solution delivery systems [9-14].

There are two different modes of fluid bed granulating

a) Wet stage: In wet stage granulation, the particles require a significant amount of moisture or granulating solution before they become tacky enough to stick to each other. The granulating solution is applied t a rate higher than the evaporating rate until the particles build up enough moisture to granulate.

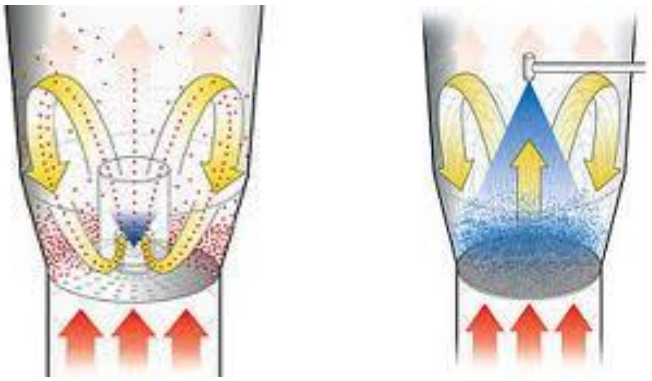
b) Dry stage granulation: In dry stage granulation, the particles require only a slight wetting to become tacky and stick to each other. The granulating solution is applied at a rate less than or equal to its evaporation rate. Thus, the particles remain "dry" through the entire process.

The particle formation in fluidized bed granulation is influenced by numerous parameters like

1. Moisture content in solids
2. Liquid spray flow rate
3. Airflow rates
4. Atomization pressure

Granulation in fluidized state can be achieved either by batch process or continuous process. For granulation in batch process, the dry starting product is placed in the product container, where it is mixed vigorously in the heated gas stream, held in the suspension and granulated by spraying with a suitable bonding material. The product is finally dried to the required end moisture content. Continuous granulators are sub-divide into several granulation zones, which are operated at different speeds and temperatures. E.g., Granulation in first and second sections, drying in the third section and cooling at the end of the process chamber.

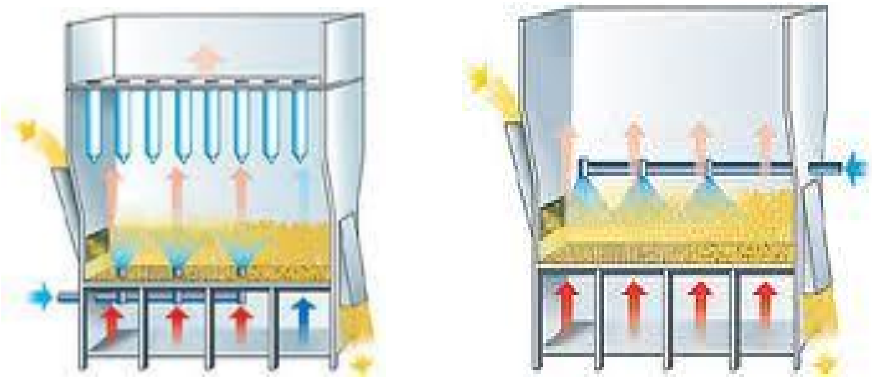
Batch process:



Bottom Spray **Top spray**

Figure 8: Fluidized bed granulation-batch process

Continuous process:



Bottom spray **Top spray**

Figure 9: Fluidized bed granulation-continuous process

Advantages:

1. Reduces dust formation during processing.
2. Improves housekeeping and worker safety.
3. Suitable for subsequent coating and controlled release products.
4. Reduces product loss.

Disadvantages:

1. Cleaning islabour-intensive and time consuming.
2. Assuring reproducibility is troublesome.

(vi) Extrusion-spheronization granulation:

The main objective of the extrusion spheronization is to produce granules or pellets of uniform size with high drug loading capacity. It is a multi step process of wet mass extrusion followed by spheronization to produce uniform sized spherical particles with narrow size distribution. Extrusion spheronization is primarily used for the production

of multiparticulates for oral controlled drug delivery system. The granules are obtained by extruding the tacky mass through extruder and subsequent spheronization using speronizer. Wet agglomeration technique involves extrusion of the wet agglomerate (tacky mass) of the powder mixture through extruder. Hot melt agglomeration technique involves extrusion of thermoplastic material through a thermostatically controlled extruder [9-14]. It is more labour intensive than other granulation method, but it is useful when uniform spherical shape, uniform size, good flow properties, high strength, low friability and smooth surface of granules is desired.

Five basic steps of extrusion-spheronization process were:

a. Dry mixing of materials to achieve homogeneous dispersion.
b. Wet/thermoplastic granulation of the resulted mixture to form wet/thermoplastic mass.
c. Extrusion of wet/thermoplastic mass to form rod shaped particles.
d. Rounding off the rod shaped particles using spheronizer.
e. Drying.

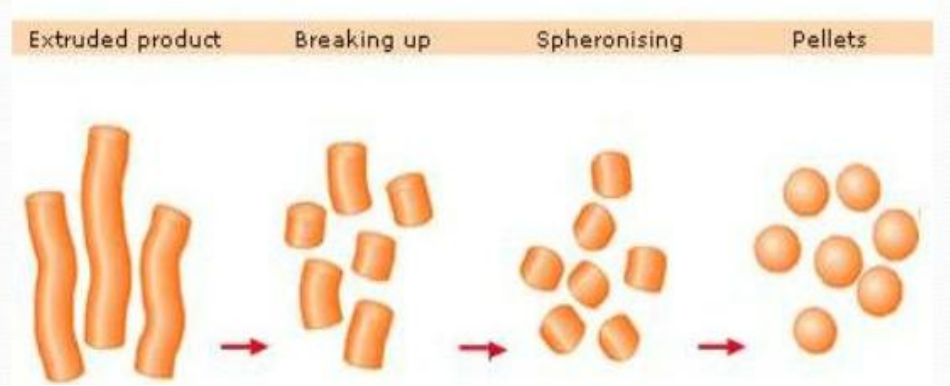


Figure 10: Different steps involved in the Extrusion- Spheronization process

Advantages:

a. Can incorporate higher levels of active ingredients without producing excessively larger particles.
b. Can easily combine two or more active agents within the same unit, in any ratio.
c. Can modify physical characteristics of the active ingredients and excipients.
d. Can produce spherical particles with high bulk density, low hygroscopicity, narrow particle size distribution and smoother surface.

Disadvantages:

1. Require more labour and time with respect to conventional granulation techniques.
2. Not suitable for moisture sensitive and thermo-labile materials.

(vii) Spray drying granulation:

In this process dry granular product is obtained by feeding a solution of active agent along with excipients into the drying system, where the feed is atomized and dried with a heated gas stream followed by separation of granular product from the gas stream. Agglomeration of particles is achieved by spraying the binder solution on the fluidized powder bed followed by drying with hot air.

Spray dried granulation improves flow and distribution of drug, colors etc, and requires less lubricant than wet massed product. Spray drying results in shell of concentrated binder at the surface of the granular material, providing strong tablets.

Figure 11: Spray granulation technique

Stages in Spray granulation:

1. Atomization of granulation liquid
2. Agglomeration of particles
3. Drying

Atomization:

It is the process in which a liquid is disintegrated into many droplets, there by yielding a high surface to mass ratio. This can be achieved by supplying energy to the liquid in the form of kinetic energy, pressure energy, centrifugal energy etc. Hydraulic pressure atomization is the most common form of atomization.

Agglomeration:

Agglomeration is facilitated by spraying the atomized granulating liquid over the particles. At low moisture content, particles contact with each other and adhere due to the formation of liquid bridges. When the liquid completely surrounds the granules droplets are formed. The surface tension of the liquid phase determines the strength of the droplet.

Drying: In this stage, heated gas is passed over the agglomerated particles to facilitate uniform evaporation of liquid from the surface of the droplets.

Advantages:

1. A rapid and continuous process.
2. Overall cost was reduced.
3. Minimizes operator exposure to dust of the product.
4. Suitable for heat sensitive product.
5. Dust free and free flowing granules with good solubility are obtained.

(viii) Freeze granulation:

The granules obtained by this method are spherical and free flowing with optimal homogeneity. Here the suspension containing powder is sprayed into liquid nitrogen, resulting in the formation of drops which are subsequently frozen to form granules and this upon freeze drying yields dry granules.

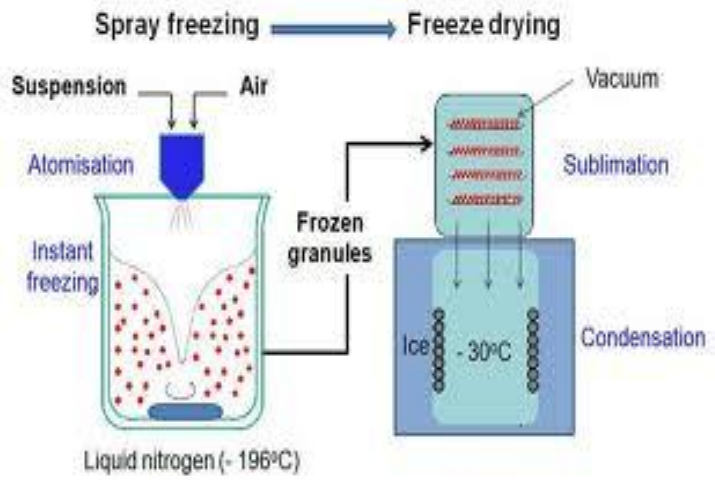


Figure 12: Freeze Granulation

Advantages:

1. Granule density can be controlled by the solid contents of the suspension.
2. Non-oxides and metals can be handled as mild drying prevents their serious oxidation.
3. Results solid granules with no cavities.
4. High yield with low material waste.
5. Low to high quantities of granule can be produced with reproducibility.
6. Equipments can be easily cleaned up.
7. Organic solvents can be recycled.

(ix) Foam binder granulation:

It is a simple and safer wet granulation technique which employs high/low shear rapid mixer granulator or fluidized bed processor. This involves continues spraying of liquid binder in the form of aqueous foam onto the blended powder bed, and after the granulation end point is achieved the wet granules are dried in fluidized bed processor until the desired moisture content is achieved. Wet foam has physical characteristics and flow similar to liquid and dry foam have high air-to-liquid ratio that moves more like a solid when used for granulation. Of these wet foam is most preferred.

Advantages:

1. Eliminates use of spray nozzle thereby eliminates plugging effects.
2. Requires low amount of the water and the binder for granulation.
3. Improves process robustness.
4. Binder distribution was uniform.
5. No over wetting.
6. Cost effective as reduces drying, manufacturing, and equipment clean-up time, and does not require new equipment or drastic changes in processing techniques.
7. Immediate release and matrix controlled-release products can be easily scaled-up.

Applications:

1. Suitable for products with very low concentration or drug level (in mg or µg per tablet) as generated foam can carry active ingredients at a very low concentration.
2. Suitable for water sensitive formulations and, highly water-soluble and even very poorly water soluble drugs.
3. Can handle historically proven difficult materials including natural ingredients used in nutritional supplements.

(x) Steam granulation:

It is a simple modification of conventional wet granulation process in which steam is used as binder instead of water. Steam is injected on to the bed of fluidized particles that are to be granulated.

Principle of Steam Granulation

Steam granulation technology involves injecting steam through one or more jets onto the fluidized bed processor contained in the hermetically airtight and thermo-stated condition. Enveloping and jacketing each jet of steam in a jet of gas that prevents premature condensing of the jet of steam into droplets thereby preventing lump formation of particle (due to powder aggregation at the water droplet formation site) in the fluidized bed processor. Alternately gas stripping system can be used. The jets of steam and gas can be injected transversely and/or axially onto the bed of fluidized particles contained in the fluidized bed processor. Coaxially the jets of steam and gas can be injected through concentric nozzles that will communicate to the interior of the fluidized bed processor. Choking of nozzle can be prevented by directing the nozzles downward or shielding or covering it, thereby inhibiting entry of fluidized particles into the nozzles which interfere with proper functioning of the apparatus. This technology permits formation of granulated product with close particle spectrum without any lumps. Hypromellose and pregelatinized starch were most frequently used binders [9-14].

Figure 13: Steam granulator

Advantages:

1. High uniformity in powder and binder distribution.
2. Diffusion rate of binder into powders is very high.
3. More spherical granule with large surface area were formed thereby increases dissolution rate of the drug from granules.
4. Favorable thermal balance results in rapid drying.
5. Time efficient as processing time was short.
6. Employs stem as binding fluid thus was environment friendly, expensive safety precautions was not required and does not results health hazards to the operator.
7. Possess regulatory compliance.
8. Can control total micro organism count.

Disadvantages:

a. Special equipments were required for steam generation and its transportation.
b. Requires high energy inputs.
c. Unsuitable for thermo-labile materials.
d. More safety measures were required.

e. Unsuitable for binders that cannot be activated by contact with stem.
f. Uses steam at a temperature of about 1500c, that tends to cause local overheating and excessive wetting of the particles in the vicinity of the steam nozzles resulting in the formation of lumps in the granulated product.

3. Conclusion

In pharmaceutical industry, most of the tablets are manufactured by either of the three methods viz. direct compression, wet granulation, dry granulation. Out of these three methods, wet granulation is the widely used method. However the choice of the method depends on the characteristics of API and other excipients used in the process. Granulation is one of the most important unit operations in the production of pharmaceutical dosage forms. These specialized granulation techniques led to the production of granules with good flow properties, compressibility, good release profile, enhanced stability and reduced the cost of production. Selection of appropriate technology for carrying out the granulation process is the key to achieve a targeted granulation and final product parameters.

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