

**TABLET GRANULATION: CURRENT SCENARIO AND RECENT ADVANCES****ABSTRACT:**

Granulation is a size enlargement process, in fine or coarse particles converted into physically stronger and larger agglomerates having good flow property, better compression characteristics and uniformity, prevent segregation of the blend components, improve content uniformity, and eliminate excessive amounts of fine particles. Size of granules has a size range of 0.2 to 4.0 mm, depending on their subsequent use. Size of the granules depends on the quantity and feeding rate of granulating liquid.

The selection of process to prepare granules requires thorough knowledge of physicochemical properties of the drug, excipients, required flow and release properties, to name a few.

At current scenario available technologies includes, spray drying, roller compaction, high shear mixing, and fluid bed granulation etc.

The objective of present work is to focus on the commonly used and novel granulation technologies like such as pneumatic dry granulation, steam granulation, moisture-activated dry granulation, thermal adhesion granulation, freeze granulation, and foamed binder or foam granulation.

**KEYWORDS:** Granulation, content uniformity, moisture activated dry granulation technology, active pharmaceutical ingredients.

**INTRODUCTION:**

Granulation Technology is the art and science for process and production of granules in which primary powder particles are made to adhere to form larger, multiparticle entities called granules<sup>1</sup>. Granules are used in production of tablets or capsules, when granules are prepared as an intermediate product and having size range between 0.2 and 0.5 mm, but larger granules are used as a dosage form in their own right<sup>2</sup>.

Granulation process commences after dry mixing of the necessary powder ingredients along with drug to achieve uniform distribution of each ingredient throughout the powder mixture. Agglomerated granules are formed by solid bridges, sintering, chemical reaction, crystallization and deposition of colloidal particles<sup>3</sup>.

After granulation the granules either packed, or they may be mixed with other excipients before tablet compaction or capsule filling.

The effectiveness of granulation depends on particle size of the drug and excipients, type of binder, volume of binder, wet massing time (less or more), amount of shear applied, drying rate (hydrate formation and polymorphism)<sup>4</sup>.

**Reasons for granulation<sup>5, 6, 7</sup>**

1. To avoid segregation of the constituents.
2. To improve the flow properties of the mixture.
3. To improve the compaction of the powder.
4. The granulation of toxic materials avoid hazard of toxic dust that may arise when handling powders.
5. To avoid formation of cake in hygroscopic substances.
6. Granules occupy less volume per unit weight so more convenient for storage or shipment.
7. To improve appearance of the product.

8. To improve compression properties of the mixture.

### **Ideal characteristics of granules<sup>8</sup>**

- It should have spherical shape for improved flow
- It should have narrow particle size distribution for content uniformity and volumetric dispensing, sufficient fines to fill void spaces between granules for better compaction and compression characteristics,
- It should have adequate moisture and hardness to prevent breaking and dust formation during process.

### **Methods of granulation:**

A. Dry granulation   B. Direct compression   C. Wet granulation

#### **A. Dry granulation<sup>9,10</sup>**

In dry granulation process the powder mixture is compressed without the use of heat and solvent.

The primary powder particles are aggregated under high pressure. There are two main processes-

i) **Slugging**- Either a large tablet known as a 'slug' is produced in a heavy-duty tableting press  
ii) **Roller compaction** or the powder is squeezed between two rollers to produce a sheet of material.

In both cases these intermediate products are broken using a suitable milling technique to produce granular material, which is usually sieved to separate the desired size fraction. Steps involved in dry granulation process are

1. Milling of drugs and excipients
2. Mixing of milled powders
3. Compression into large, hard tablets to make slug
4. Screening of slugs
5. Mixing with lubricant and disintegrating agent
6. Tablet compression

#### **Advantages:**

1. It uses less equipments and space.
2. It eliminates the need for binder solution, heavy mixing equipment and the costly and time consuming drying step required for wet granulation.
3. Slugging can be advantages for moisture and heat sensitive materials and improved disintegration since powder particles are not bonded together by a binder.

#### **Limitations-**

1. It requires a specialized heavy-duty tablet press to form slug.
2. It does not permit uniform color distribution as can be achieved with wet granulation where the dye can be incorporated into binder liquid.
3. The process tends to create more dust than wet granulation.

#### **B. Direct compression<sup>11</sup>:**

This method is used when ingredients can be blended and placed in a tablet press to make a tablet without any of the ingredients having to be changed. However 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

Direct compression involves following steps:

1. Milling of drug and excipients
2. Mixing of drug and excipients
3. Tablet compression

#### **Advantages-**

1. It is more economic since the direct compression requires few unit operations.
2. More suitable for moisture and heat sensitive drugs.
3. The tablets prepared by direct compression exhibits comparatively faster dissolution.
4. Less wear and tear of punches.

**Disadvantages:**

1. Capping, lamination, splitting, or layering of tablets is sometimes related to air entrapment during direct compression.
2. When air is trapped, the resulting tablets expand when the pressure of tablet is released, resulting in splits or layers in the tablet.
3. In some cases, require greater sophistication in blending and compression equipments. Direct compression equipments are expensive.

**3. Wet Granulation<sup>12</sup>:**

Wet granulation process involves wet massing of the powder blend with a granulating liquid, wet sizing and drying. The fluid contains a solvent which must be volatile so that it can be removed by drying, and be non-toxic. Typical liquids include water, ethanol and isopropanol, either alone or in combination.

**Steps involved in the wet granulation**

1. Mixing of the drugs and excipients
2. Preparation of binder solution
3. Mixing of binder solution with powder mixture to form wet mass.
4. Coarse screening of wet mass using a suitable sieve (6-12 screens).

**Advantages<sup>13</sup>:**

1. It allows mechanical handling of powders without loss of quality of blend.
2. The flow properties of powder are improved by increasing particle size and sphericity.
3. Increases and improves the uniformity of powder density.
4. Improves cohesion during and after compaction.
5. There is reduction of air entrapment.
6. Less dust and cross contamination.
7. The hydrophobic surfaces are made hydrophilic.

**Limitations of wet granulation:**

1. It is an expensive process because of labor, time, equipment, energy and space requirements.
2. Loss of material during various stages of processing
3. Not suitable for moisture sensitive or thermo labile drugs
4. It involves multiple processing steps add complexity and make validation and control difficult
5. Incompatibility between formulation components is aggravated.

**ADVANCED GRANULATION TECHNIQUES-**

**1. Melt agglomeration/ thermoplastic granulation<sup>14</sup>:**

This technique consists of the agglomeration of powder particles using binders that, which melts or softens at relatively low temperature (50–90 °C). Solid fine particles are bound together into agglomerates by agitation, kneading, and layering in the presence of molten binding liquid.

After cooling of the agglomerated powder and the consequent solidification of the molten or soften binder complete the formation of the granules.

It utilizes two methods one is spray on method that 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. Another one is in situ melt granulation method that employs a solid binder which is heated above its melting point by hot air, when it is processed in fluidized bed processor.

### Advantages:

1. No requirement of any solvent either aqueous or non-aqueous.
2. Less time consuming and economical process.
3. Uniform dispersion of fine particle.
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. Improved product stability.

### Disadvantages:

1. Not suitable for thermo-labile materials.
2. There is need of high energy input.
3. During handling and storage of agglomerates melting or softening of binder may occur.

### (2) Foam granulation<sup>15</sup>

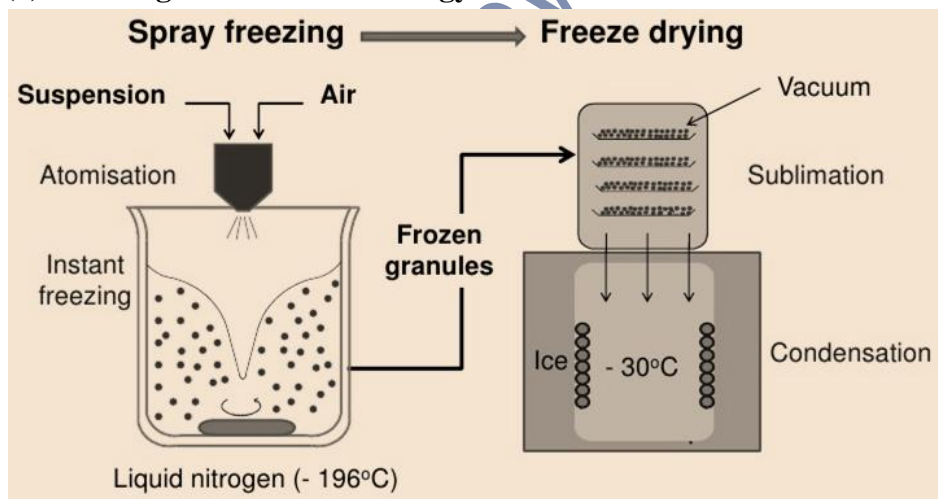
This technique is analogous to spray agglomeration; it involves the addition of liquid/aqueous binder as foam instead of spraying or pouring liquid onto the powder particles. Adding the binder solution as foam rather than a spray eliminates the problems of inconsistent and unpredictable binder distribution that can affect tablet hardness and drug release.

A foam generator is used in the binder solution tank with high-shear granulator or fluid bed granulator to introduce the binder as foam rather than spraying or pouring in binder onto the moving powder particles.

### Advantages-

1. No need of spray nozzle.
2. Less water required
3. Economical process
4. Suitable for water sensitive formulations.

### (3). Freeze granulation technology<sup>16</sup>:



### Freeze Granulation

This technique enables preservation of the homogeneity from suspension to dry granules. By spraying a powder suspension into liquid nitrogen, the drops are instantly frozen into granules, and by freeze drying process, the granules are dried by sublimation of ice without any segregation effects. The result will be spherical, free flowing granules, with optimal homogeneity.

### Advantages-

1. Granule density can be controlled by the solids content of the suspension.
2. Cavities in the granules can be avoided.

3. High yield, less wastage of material.
3. Easy cleaning of equipments.
4. Organic solvents can be recycled.

#### **(4) Moisture activated dry granulation<sup>17</sup>**

This technique is a variation of conventional wet granulation technique. This 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, potato starch, a mixture of MCC and potato starch (50% w/w to remove excess of moisture present in the granulate. The moisture absorbents absorb the moisture from the agglomerates, resulting in moisture redistribution within the powder mixture, leading to relatively dry granule mixture.

This process is accomplished by two major steps agglomeration and moisture distribution. It involves the formation of wet mass by using granulating fluid and then utilizing the moisture absorbing materials to dry the granules.

#### **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  $\mu\text{m}$ ) 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.
6. Applicable to more than 90% of the granulation need for pharmaceutical, food and Nutritional industry.

#### **Disadvantages:**

1. Unsuitable for thermo-labile, moisture sensitive, high moisture absorbing substances.
2. Formulations with high drug loading are difficult to develop.

#### **(5) Extrusion-spheronization granulation<sup>18</sup>:**



**Figure 2: Extrusion Spheronizer**

This technique involve in production of granules or pellets of uniform size with high drug loading capacity. It consist of multiple steps of wet mass extrusion followed by spheronization to produce uniform sized spherical particles with narrow size distribution.

It is mainly used in multi particulates for oral controlled drug delivery system.

Steps involved in extrusion-spheronization process:

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

**Advantages:**

- a. Suitable for higher levels of active ingredients without production of larger particles.
- b. Suitable for combination of two or more active agents within the same unit, in any ratio.
- c. It produces spherical particles with high bulk density, low hygroscopicity, narrow particle size distribution and smoother surface.

**Disadvantages:**

1. Time consuming process having requirement of more labour.
2. Moisture sensitive and thermo-labile materials are not suitable candidates for it.

**(6) Fluidized bed granulation<sup>19</sup>:**

It is an air suspension technique in which binder solution is sprayed on to the fluidized powder bed in order to get finer, free flowing and homogenous granules. This fluidized bed processor contains air handling unit, product container, air distributor, spray nozzle, disengagement area, process filters, exhaust blower/fan, control system, and solution delivery systems.

The particle formation in fluidized bed granulation is influenced by numerous parameters like moisture content in solids, liquid spray flow rate, airflow rates, and 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.

**(7) Spray drying granulation<sup>20</sup>:**

This process is used to produce microcapsules, food ingredients, flavors and various biotechnological preparations. 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. This process differs from other methods in that it is a continuous process in which a dry granular product is made from a solution or a suspension rather than initially dried the primary powder particles.

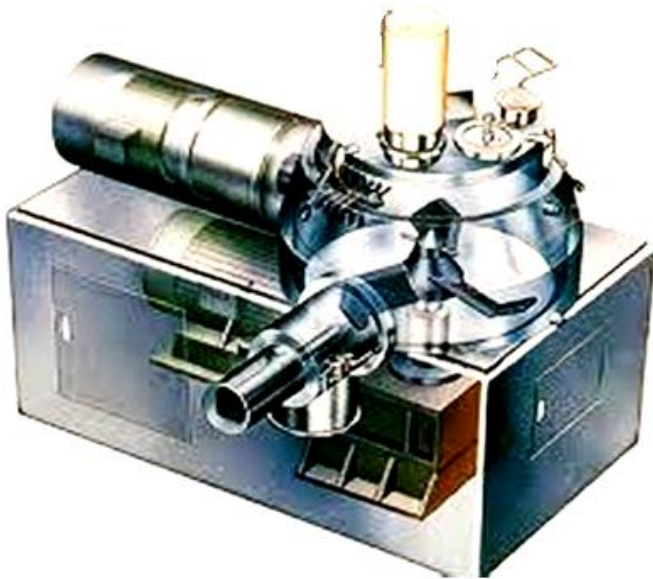
The spray drying process involves three fundamental steps,

1. Liquid feed's atomization into fine droplets
2. Mixing of spray droplets with a heated gas stream, for liquid evaporation.
3. Separation of the dried powder from the gas stream.

**Advantages:**

1. It is a rapid and continuous process
2. It reduces overall cost by eliminating labor intensive drying and granulation steps.
3. Less exposure to dust.
4. Heat sensitive products are suitable candidates.

**(8). Steam granulation**



### **Steam granulator**

This process is simply a modification of conventional wet granulation method. In this technique, water steam is used as binder. Pure form of steam is transparent gas, and it provides a higher diffusion rate into the powder and a more favorable thermal balance during the drying step. At standard temperature and pressure, pure steam (unmixed with air, but in equilibrium with liquid water) occupies about 1,600 times the volume of an equal mass of liquid water. After condensation of the steam, water forms a hot thin film on the powder particles, requiring only a small amount of extra energy for its elimination, and evaporates more easily.

#### **Advantages:**

1. Results in more spherical granule formation
2. Higher diffusion rate
3. Environment friendly, safe for working operator.
4. Maintain sterility

#### **Disadvantages:**

1. There is need of special equipment for steam generation and transportation.
2. Need of high energy inputs
3. Not suitable for thermo labile materials.

### **(9). Thermal adhesion granulation:**

This technique was developed by Wei-Ming Pharmaceutical Company (Taipei, Taiwan). It involves granulation of the blend by addition of very less amount of water or solvents.

This technique is quite simple and convenient with low moisture and binder contents in a closed system for preparing highly compressible materials or for modifying the poor characteristics of excipients.

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 90°C-105°C in case of water and 70°C-90°C in case of ethanol, and mixed under tumble rotation for 3-20 minutes until the granules are formed.

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<sup>21</sup>.

#### **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 tableting properties.

3. Minimizes the dust generation during powder processing.

**(10) Pneumatic dry granulation<sup>22</sup>:**

This method involves production of granules from powder particles by initially applying mild compaction force by roller compactor to produce a compacted mass comprising a mixture of fine particles and granules. To separate the granules and to recycle the rejected fraction, a newly innovated fractionating device is employed. Granules pass through the fractioning chamber to be compressed into tablets. Pneumatic dry granulation is suitable for automatic or semi-automatic production of granules.

**Advantages:**

- a. High drug loading is possible.
- b. Faster development (within weeks).
- c. Suitable for thermo-labile and moisture sensitive drugs.
- d. Improved stability with increased shelf-life.
- e. Compatible with other technologies like coating, sustained release.
- f. Produce soft and porous granules with improved flow property and compressibility.
- g. Taste masking can be achieved.
- h. Sterile products and toxic materials can be handled.
- i. Reduces cost of final product by minimizing waste through recycling and production cost.

**Characterization methods of granules.**

S.N.	Parameters	Method
1.	Particle morphology	Optical microscopy
2.	Granule flow ability and density	Density apparatus, mechanical and Hopper method
3.	Particle size distribution	Sieve analysis, laser light scattering
4.	Granule porosity	Mercury intrusion methods
5.	Thermal analysis	DTA, TGA, DSC
6.	Nature	Powder X-ray diffraction
7.	Identification	Near-Infrared spectroscopy (NIR)
8.	Surface area	Gas adsorption

**CONCLUSION:**

Granulation is one of the most important unit operations in the production of pharmaceutical dosage forms. It is used to prevent segregation of formulation components in a powder blend, bulk volume of granulation, improve blend flow, content uniformity, compressibility, and other properties.

In pharmaceutical industry, tablets are manufactured by either of the three methods viz. direct compression, wet granulation, dry granulation. Each technique has its own advantage and disadvantages. Selection of correct granulation method depends on the ingredients individual characteristics and ability to properly flow, compresses, eject, and disintegrate. Choosing a method requires thorough investigation of each ingredient in the formula, the combination of ingredients, and how they work with each other.

Selection of appropriate technology for carrying out the granulation process is the key to achieve a targeted granulation and final product parameters. So, depth knowledge of the processing



techniques and their merits and demerits is required to adopt during development stage of product.

This review discussed the recent developments in granulation technology; it may be beneficial for many researchers to work at development of granules for various dosage forms like tablets and capsules.

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