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Granulation

Prathmesh Sirame¹, Rajeshwari Khairnar², Rupali Tasgaonkar³

^{1, 2, 3}Bachelor of Pharmacy, Department of Pharmaceutics

Abstract: Granulation is one of the most important unit operations in the production of pharmaceutical oral dosage form. It is the process in which primary powder particles are made to adhere to form larger multiparticle entities called granules. The Granulation process will improve flow and compression characteristics, reduce segregation, improve content uniformity, improve density and eliminate excessive amounts of particles. Improved yields, decreased tablet defects, higher productivity, and decreased downtime will be the outcomes. All across the world, pharmaceutical products are processed utilising the direct compression, wet granulation, or dry granulation techniques. The process is determined by the properties and capacity of each element to appropriately compress, expel, and disintegrate. The review article provides the most recent technological breakthroughs. This review provides an overview of them along with a brief explanation of each development's importance and limits. Each drug material provides a different problem during formulation creation, which the scientists working on the process must take into account at the process selection stage.

Keywords: Granulation technology ,Pneumatic Dry Granulation, Freeze granulation, Foam granulation, Steam granulation ,Thermal Adhesion Granulation

I. INTRODUCTION

By forming links between them, particles are gathered together in a process called granulation. Bonds are created either through compression or the use of a binding agent. [1] In the pharmaceutical business, the granulation process is frequently used to prepare materials for tableting. Micro-encapsulation, multi-particulate systems for customised release mechanisms, and the preparation of granules for patient use directly are further processes that involve granule production. Granules are manufactured primarily to enhance the blend's flow and compression characteristics. However, there are a variety of other factors that might contribute to granulation, including

- 1) Improving flow properties of the mixture and also improving the uniformity of the dose;
- 2) Increasing product's bulk density
- 3) Making metering or volumetric dispensing easy;
- 4) regulating the rate of drug release;
- 5) Decreasing the dust production and reduce worker exposure to drug products;
- 6) Improving the appearance of the products. [2]

The size of pharmaceutical granules normally ranges from 0.2 to 4.0 mm, depending on their intended usage [3]. When used as a dosage form, the granules will either be packed or they may be combined with additional excipients before tablet compaction or capsule filling. [4] One of the most important unit operations in the manufacture of pharmaceutical dosage Forms, primarily tablets and capsules, is granulation, a technique of particle expansion by agglomeration [5] Small, coarse or fine particles are combined into enormous agglomerates known as granules during the granulation process. In order to obtain a uniform distribution of each Ingredient throughout the powder combination, granulation typically starts after the initial dry mixing of the required Powder ingredients and the active pharmaceutical Ingredient (API). Despite having a particle size range of 0.2-4.0 mm, granules employed in the pharmaceutical industry are primarily generated as an intermediary with a size range of 0.2-0.5 mm to be either packed as a dosage form or be Mixed with other excipients prior to tablet compaction or capsule filling. [5][6]

Granules are produced in order to improve the uniformity of the API in the finished product, to increase the blend's density so that it takes up less space per unit weight for better storage and shipment, to simplify metering or volumetric dispensing, to reduce dust during the granulation process to reduce toxic exposure and process-related hazards, and to improve the product's appearance [6]. As a result, spherical shape for improved flow, narrow particle size distribution for content uniformity and volumetric dispensing, and enough fines to fill in the spaces between granules for better compaction and compression are the ideal properties of granules.[7] The properties of the particles of the granules are depends on the drug's particle size and the excipients, The type, volume, and/or concentration of the binder and/or solvents, as well as the granulation duration, granulator type, and drying rate (temperature and time) [7].

Solid bridges, sintering, chemical reactions, crystallisation, and the deposition of colloidal particles are some of the main processes that lead to the formation of agglomerated granules [5] [8]. Additionally, binding can be carried out through adhesive and cohesive forces when using high viscosity binders. A number of processes, including wetting and nucleation, coalescence or growth, consolidation, and attrition or breakage, are involved in the formation of granules from powder particles. [8] Powder mixtures containing pharmaceutical excipients and API can either be crushed directly into tablets or after granules were made using the agglomeration or granulation procedure. [fig 1]

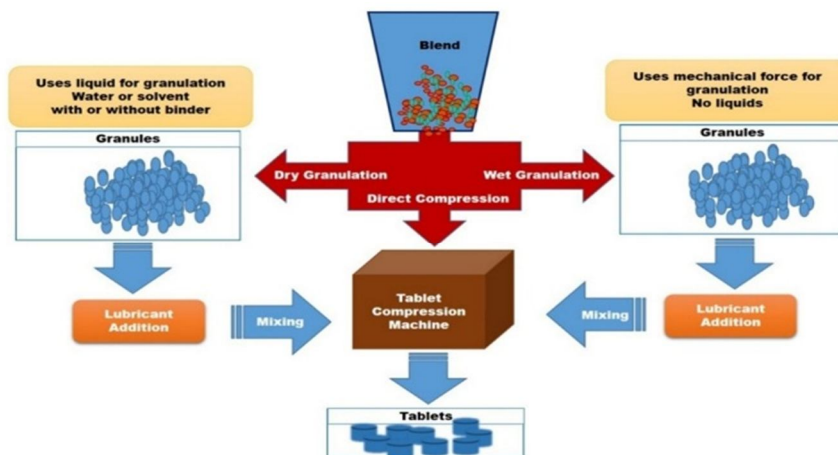


Fig. 1 Schematic diagram of tablet compression techniques [7]

Granulation Technology can be broadly divided into 3 types based upon the type of processing involved

A. Dry Granulation

Due to its ease of use and economic effectiveness, dry granulation is a simple and growingly common approach. Methods available to improve dissolution include Salt formation, micronization and addition of solvent or surface-active agents [10]. The main Powder particles are aggregated at high pressure in the Dry Granulation Method. two basic procedures: either the powder is crushed into a huge tablet (known as a “slug”) using a heavy-duty tableting press, or the powder is squeezed between two rollers to produce a Sheet of material (roller compaction) [11]. Dry granulation involves granule formation without using liquid solution as the product may be sensitive to moisture and heat. [1]

Tab. 1 Advantages and disadvantages of dry granulation [9]

Advantages	Disadvantages
For materials that need to be dry	To form SLUG, you need a specialised, heavy-duty tablet press.
For materials that react to heat	It does not allow for the uniform colour distribution that can be achieved with wet granulation, in which the dye can be mixed with the binder liquid.
Because powder particles are not joined by a binder, disintegration is improved.	The method typically produces more dust than wet granulation, which raises the risk of contamination.

RECENT DEVELOPMENTS IN DRY GRANULATION

Dry granulation could be accomplished using slugging or roller compaction. The schematic graphic illustrates the two distinct types in fig 2. Compared to wet granulation, there hasn't been much advancement in dry granulation technique or technology. [7]

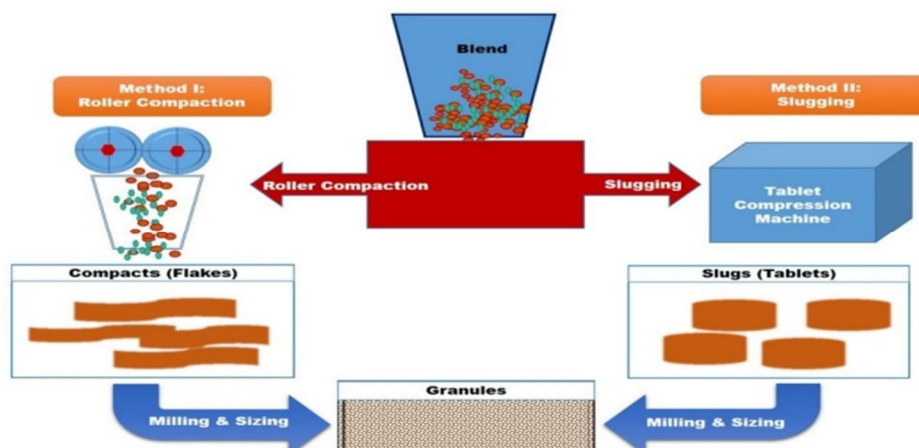


Fig. 2. Schematic diagram of dry granulation and two different Techniques. Method I is roller compaction and Method II is Slugging.[7]

1) Pneumatic Dry Granulation (PDG)

The PDG Technology is based on a novel dry process for automatic or semi-automatic granule production called pneumatic dry granulation. It Enables flexible modification of drug load, Disintegration time and tablet hardness, can achieve High drug loading, even with ‘difficult’ APIs and Combinations. It is used for For Taste masking, For Excellent stability,It Is works with other technologies, such as Sustained release, fast release, coating . This method Is suitable for heat labile and moisture sensitive Drugs, and the subject of a number of patent applications.The PDG Technology produces porous granules with Excellent compressibility and characteristics of the flow ability [4]

By utilising roller compaction and a unique air classification strategy, pneumatic dry granulation (PDG), a cutting-edge dry granulation technique, creates granules with an exceptional combination of flowability and compressibility.[10] [11] To create a compacted mass with a mixture of granules and small particles, powder particles are first lightly crushed in a roller compactor. a roller compactor, powder particles are first lightly crushed to produce a compacted mass that contains a mixture of granules and small particles. While the fine particles and/or smaller granules are separated from them by entraining in a gas stream, the necessary size granules pass through a fractioning chamber to be crushed into tablets (pneumatic system). whereas the fractioning chamber is where the granules of the desired size pass before being crushed into tablets. The entrained small granules and/or fine particles are then transferred to a device, such as a cyclone, and are either returned to the roller compactor for immediate re-processing (recycling or recirculation process), or they are placed in a container for re-processing later to produce the desired size granules.[12] [13] The process’ schematic diagram is shown below in fig 3.

In order to successfully create good flowing granules for any formulations that result in compacts with a tensile strength of less than 0.5 MPa, PDG technology could be applied. Additionally, because sufficient flowability may be attained even at lower roll compaction strengths (lower solid fractions) than normal roller compaction, this approach makes it possible to use high drug loading of up to 70–100%.[7]

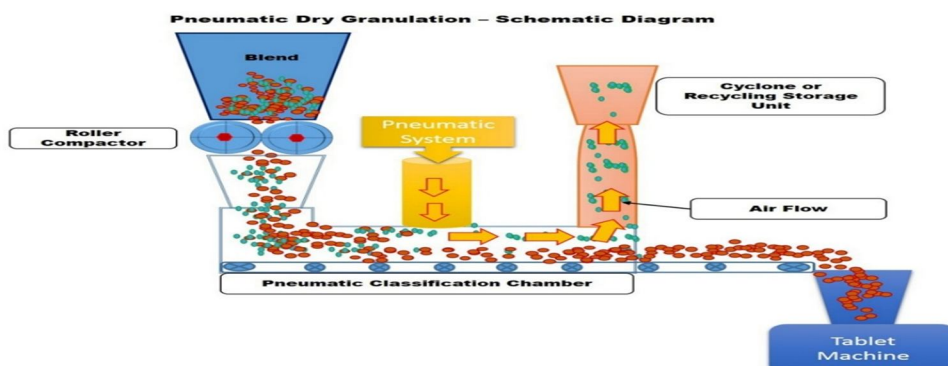


Fig. 3. Schematic diagram of pneumatic dry granulation

Advantages of PDG Technology [4]

- a) Even with materials known to be historically difficult to handle, good granulation outcomes have been obtained at high drug loading,
- b) Faster manufacturing than wet granulation
- c) a closed system that provides safety benefits due to reduced dust levels
- d) the opportunity for sterile production, or the handling of dangerous compounds,
- e) The granules and tablets produced exhibit fast disintegration properties, providing the potential for Fast release dosage forms, and Release time can be adjusted to requirements.
- f) There is less material waste.

The primary Powder particles are aggregated at high pressure in the dry granulation process. the powder is compressed between two rollers to create a sheet of material (rolling compaction) or a huge tablet (known as a slug) is produced in a powerful tableting press (a process known as slugging) [11]

The two distinct Types are shown below.

- *Slugging Process:* Granulation by slugging is the technique of compressing dry powder used to make tablets using a tablet press with a die cavity that has a large enough diameter to fill fast. Accuracy or slug condition aren't very crucial. Use only the amount of pressure necessary to condense the powder into even slugs. Slugs are created, then after screening and milling they are reduced to the proper Granule size for final compression.[11]
- *Roller Compaction:* A device known as a chilsonator can also be used to compact powder using pressure rolls. In contrast to a tablet machine, a chilsonator produces a compressed material in a steady, uninterrupted flow. From the hopper, which has a spiral auger to feed the powder into the compaction zone, the powder is fed down between the rollers. The aggregates are screened or processed to create granules, just like slugs. [14]

The dry granulation process involves the following steps: [14]

- Milling of drugs and excipients
- Combining ground-up powders
- Create slug by compressing into large, hard tablets.
- Slug screening
- Blending with a lubricant and an agent to dissolve
- Compression of tablets

B. *Wet Granulation*

Using a granulating fluid, wet granulation entails massaging a mixture of dry primary Powder particles. The solvent in the granulating fluid must be volatile in order to be removed by drying. Water, ethanol, and isopropanol are common liquids that can be used singly or in combination. Traditional wet granulation methods included fluid bed, high shear, and low shear granulation.[15]

Tab.2 advantage and disadvantage of wet granulation

Advantages	Disadvantages
The cohesiveness and compressibility of powders are enhanced	Several steps.
Uniform distribution	Long length
A large variety of powders can be possessed together in a one batch.	Requires a variety of equipment the potential for significant material loss due to the transfer phases
Controlled release dosage form can be accomplished by the selection of appropriate binder and solvent.	Duration of time is greater

Conventional wet granulation method includes

1) *Low Shear Granulation*

It is the traditional method of making granules. Four equipment are mainly used in this case:

- a) Mixer machine to mix the ingredients, however when the formulation containing two to three components with equal amounts can be avoided this equipment and can be done in the planetary mixer
- b) Planetary mixer to make the wet mass or paste
- c) Oscillating to make the wet granules
- d) Dryery the wet granules (Tray dryer or fluidized Dryer) [14]

Table 3: Low shear Granulation

Advantages	Disadvantages
The process is not very sensitive to changes in the characteristics of the granule's ingredients.	Multiple steps, long duration.
The end point of the massing process can often be determined by inspection	The need for several pieces of equipments, The high material loss that can be incurred because of transfer stages.

2) *Shear Mixture Granulation*

In the pharmaceutical industry, high shear mixtures are frequently utilised for blending and granulation. High mechanical agitation is added to blending and wet massaging by an impeller and a chopper. Through shear and compaction force applied by the impeller, mixing, densification, and agglomeration are achieved.[14]

In a high-shear mixer, wet agglomeration typically involves 3 parts [1]

- a) Mixing Dry Powder (2 to 5 minutes)
- b) Adding liquid binder (Approx 1-2 mins)
- c) Using wet mass

The wet mass is created, and then it undergoes additional processing to generate dry grade particle size Granules.[1]

- Granule wet sieving
- Drying
- Dry granule sieving

Tab. 4 Advantages and disadvantages of shear mixture granulation

Advantages	Disadvantages
Short processing time.	High-shear granulator produces less compressible granules when compared to low-shear granulator.
fewer liquid binders are needed than with a fluid bed.	The creation of big lumps may result from overwetting the granules.
Granulated material can be produced from highly cohesive material.	Thermolabile materials might undergo chemical deterioration as a result of temperature rise.

3) *Fluid_Bed Granulation*

The process of fluidization involves contacting a gas with fine particulates to change them into a fluid-like state. The fluid will support the particles at a specific gas velocity, allowing them to move freely without becoming trapped.

Granules are created in a single piece of equipment using the fluid bed granulation technique, which involves spraying a binder solution onto a fluidized powder bed. The substance going through the fluid bed Finer, more uniform, and free-flowing granulation. In the system, air is heated before being forced through the item to be treated. Later, the same air is released through the product's Voids.[16] Wurster was the first to describe fluid bed processing of pharmaceuticals by using air suspension technique to coat tablets. Later, this technique was used in the granulation and drying of pharmaceuticals [1] for the creation of compressed tablets. The fluidized bed system includes a number of parts, including

- a) Air-Handling Unit (AHU)
- b) Product Container and Air Distributor
- c) Spray Nozzle
- d) Disengagement Area and Process Filters
- e) Exhaust Blower or Fan
- f) Control System
- g) Solution Delivery System.

Presents a typical fluid bed granulator (Glatt Type)

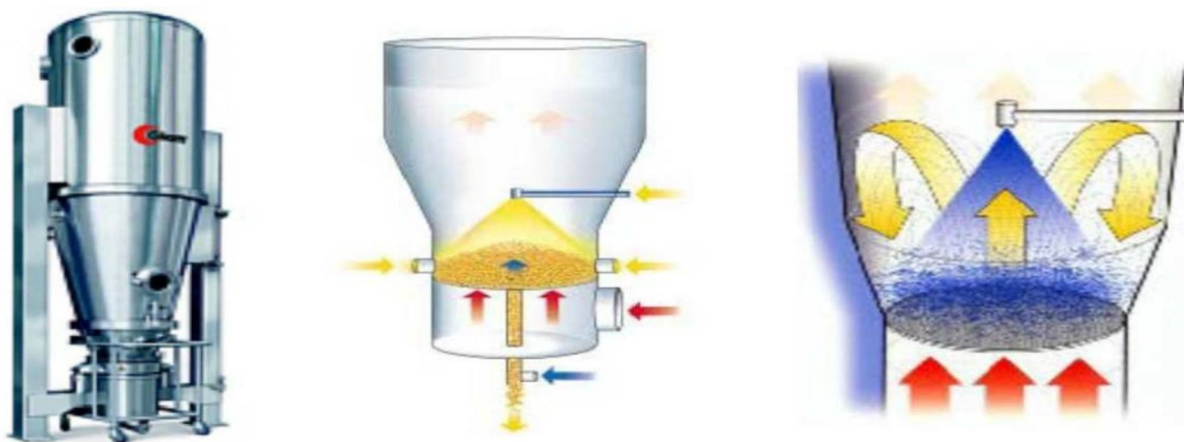


Fig.4 Fluidized Bed Granulator (Glatt)

Tab.5 advantages and disadvantages

Advantages	Disadvantages
It lessens the formation of dust during processing, which enhances housekeeping	The Fluid Bed cleaning is labor-intensive and time-consuming process
Product loss is reduced	Difficulties in assuring reproducibility.
workers safety has been improved	

RECENT PROGRESS IN WET GRANULATION:

- **Reverse Wet Granulation:** The typical granule nucleation process was eliminated by the development and study of the reverse wet granulation technique, which involves dipping dry powder into the binder liquid. The risk of uncontrolled growth and batch loss is lowered as the Reverse-phase process moves in the direction of reduced liquid saturation. By enabling consistent binder distribution, it enhances the properties of weakly water-soluble drugs dissolution [17]. Breakage of big moist agglomerates and mechanical dispersion of the binder liquid throughout the powder formulation were the main mechanisms of the reverse-phase granulation process. The liquid saturation and impeller speed regulate the size and porosity of reverse-phase granules, and the dimensionless Stokes deformation number and the growth Regime map are the best indicators of these physical characteristics [18]. Merits of Reverse Wet Granulation over Conventional Wet Granulation [14]
 - by enabling homogeneous distribution of the binder, improves the features of poorly water-soluble medicines' dissolution. Additionally, particles' better flow characteristics.
 - Increases the likelihood that the medication and hydrophilic polymer will make adequate and uniform contact, resulting in improved dissolution.
 - Uniform wetting and erosion of the granule

- **Steam Granulation:** In steam granulation technique steam is used as a binder Instead of water [3]. A steam granulation process contains the injection of a jet of steam into a bed of fluidized particles that has to be granulate. To prevent the premature condensation of the steam onto the fluidized particles and/or the condensation of the Steam, the jet of steam is substantially surrounded by a jet of air. onto the neigh boring walls of an apparatus employed to Fluidize the particles, thereby this process inhibits excessive Wetting and lumping of the particles during their granulation

Tab.6 advantages and disadvantages of steam granulation

Advantages	Disadvantages
Uniformly distributed in the powder particles	Requires special equipment for Steam generation and Transportation
Higher diffusion rate	Thermo labile materials are Poor candidates.
Health hazards	More safety measure required
In more Spherical granule Formation.	Not suitable for all the binders
sterility	

- **Moisture-Activated Dry Granulation (MADG):** In the moist granulation technique (MGT), a minimum amount of liquid is used to activate a binder in a planetary mixer [19]. Then, any excess moisture is absorbed by the addition of a Moisture-absorbing substance. When compared to direct compression, moist granulation produced larger particles; these results are comparable to those from typical wet granulation after drying and screening. For this formula, moist granulation appears to be comparable to conventional wet granulation based solely on particle size. The development of controlled-release formulations appears to be possible with the moist granulation approach [19] [20] Without using heat to dry the granules, moisture is employed in MADG to stimulate granule production. MADG can be processed continuously. There are basically two phases in MADG [21]

- Agglomeration
- Moisture absorption and dispersion

Benefits

- More than 90% of the granulation requirements for the food, pharmaceutical, and nutritional industries are applicable.
- Time-effective.
- Conducive to continuous processing
- Processing requires less energy.
- Drawbacks
- APIs that are highly moisture absorbing and moisture sensitive are poor candidates.

- **Thermal Adhesion Granulation (TAG):** Similar to moist granulation, it uses heat and a little amount of granulation liquid to agglomerate the particles. As the granulation liquid in this procedure, both water and solvent are used. Heat is also employed to speed up the granulation process. To aid in the agglomeration of the powder particle, the drug and excipient mixture is heated to a temperature of 30-130° C in a closed system while being rotated [22]. Due to the addition of a little amount of granulation liquid, which is primarily consumed by the powder particles during agglomeration, this technology eliminates the drying process. After cooling and sifting, granules with the desired particle size can be obtained. It can be used to make formulations for direct tableting [14][22]

- **Melt Granulation:** Pharmaceutical powders are effectively agglomerated by a Meltable binder using the melt granulation technique. The benefit of this method over traditional granulation is the absence of the requirement for organic solvents or water. The procedure takes less time and uses less energy than wet granulation. since there is no drying step. For materials that are sensitive to water, melt granulation is a suitable substitute for other wet granulation processes. Pharmaceutical companies presently use the melt granulation technique to create a number of dosage forms and formulations, including immediate release and sustained Release pellets, granules, and tablets. [14]

Tab 7. Advantages and disadvantages of melt granulation

Advantages	Disadvantages
Time and money efficient.	Lower melting point Binder could dissolve / soften whenever is handled or Storage
Controlling and modifying the release of drugs.	Heat sensitive materials Are poor candidates, which is a drawback
Drugs that are Water sensitive are good candidates	

- *Freeze Granulation:* Spraying liquid slurry or suspension droplets into liquid nitrogen, followed by freezing and drying the frozen droplets, is the process used in freeze granulation technology. Spraying a powder suspension into liquid nitrogen causes the drops to rapidly freeze into granules, which are then dried by ice sublimation without any segregation effects during the subsequent freeze-drying process [19][20].

Advantage:

- Able to prepare granules without cavities and adjust the granule density using the solid content of the suspension
- for the creation of granules from suspensions whose homogeneity and particle size must be maintained.
- Reduce organic compound damage and increase solubility or stability.
- High product yield since there is little material loss
- Recyclability of organic solvents

- *Foam Granulation:* Involves adding a liquid or aqueous binder in the form of foam rather than spraying or pouring liquid on the powder particles. It costs less money and uses less water because there is no spraying nozzle. Air is added to a common water-soluble polymeric excipient's binder as METHOCEL using a straightforward foam generating device [21,22].

Advantages:

- There is no spray nozzle
- Improve process robustness
- Less water required for granulation
- time-effective drying
- Cost-efficient
- Even binder distribution
- Useful for formulations that are water sensitive.

C. Direct Compression

The tableting of a mixture of ingredients, or the compression mix, without the use of a preliminary granulation or aggregation step is known as direct compression (sheskey et al., 2003) The active pharmaceutical ingredients (API) are combined with one or more excipients in the compression mix. Binders, fillers, diluents, disintegrants, and lubricants are examples of excipients. DC compression mixes must be uniformly flowing into the die and form a robust tablet (Thejaswini et al., 2013) The majority of tablet manufacturing prior to the 1960s involved granulating the powdered components before tableting. Granulation is mostly used to create free-flowing compression mixes with acceptable compactability. Railmkar et al (2000) The development of DC was made possible by the availability of DC grade excipients and quicker tablet computers with aided feed and precompression.

In 1962, Milosovitch gave the first important presentation of the DC idea. Distinction between DC and wet or dry granulation is not always well defined since adding extragranular components (also known as “post-granulation running powder”) is considered a DC step even though the granulate itself can be considered one of the DC ingredients. The use of microcrystalline cellulose (MCC) post-granulation to improve tablet hardness is important because granulation does not always offer the desired Compact ability. Has become customary since the creation of DC. Wet/dry granulation and DC share the unit processes of blending and compaction. (Sarath et al., 2011) [9]

1) Advantages of Direct Compression:

- a) Economic Efficiency
- b) Consistency

- c) Quicker Dissolving
 - d) Less punch wear and tear
 - e) Simple Validation
- 2) Limitations of direct compression:
- a) separation
 - b) potentials for diluting
 - c) Functionality variations
 - d) Lubricant sensitivity
 - e) Reusability

II. CONCLUSION

Technical and technological advancement that helps in Development and ease other facilities is always desirable. It is obvious that, the pharmaceutical granulation method and Technologies have improved over the years. However, the pharmaceutical companies have always had a particular interest in efficient and affordable manufacturing techniques, which aids in the advancement of their global research and development. Each drug material poses a different problem during formulation development, which the formulation development scientists must take into account while choosing the technique. In addition to the granulation techniques and technologies themselves, choosing the right technique and technology requires in-depth knowledge of the drug's physicochemical properties, excipients, necessary flow and release properties, etc. Each technique has some advantages and disadvantages. The review article's goal is to provide thorough information in this area that will be helpful to scientists and researchers working on new products.

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