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Granulation techniques & its updated modules

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Abstract

Granulation is the process in which primary powder particles are made to adhere to form larger multi-particle entities called granules. Granulation is required to avoid segregation, enhance the flow of powder, to produce uniform mixture, to produce dust free formulation, to eliminate poor content uniformity and to improve compaction characteristics of mix. Granulation method is mainly divided into two types: wet granulation and dry granulation. Like any other scientific field, pharmaceutical granulation technology also continues to change, and arrival of novel and innovative technologies are inevitable. This review focuses on the recent progress in the granulation techniques and technologies such as pneumatic dry granulation, reverse wet granulation, steam granulation, moisture-activated dry granulation, thermal adhesion granulation, freeze granulation, and foamed binder or foam granulation. This review gives an overview of these with a short description about each development along with its significance and limitations. During the formulation development, each drug substance poses a unique challenge that must be taken into consideration at the process selection stage by the formulation development scientists.

Keywords: Granulation, reverse wet granulation, moisture-activated dry granulation, steam granulation, melt granulation, foam granulation, roller compaction

Introduction

Granulation is the process in which primary powder particles are made to adhere to form larger multi-particle entities called granules. Pharmaceuticals granules typically have a size range between 0.2-4.0 mm, depending on the subsequent use of the granules [1]. Although granules used in the pharmaceutical industry have particle size in the range of 0.2-4.0 mm, they are primarily produced 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 before tablet compaction or capsule filling [2].

Pharmaceutical granulation is the rapid breakdown of agglomerates, are important to maximize the available surface area and aid in solution of the active drug. In ancient times the granulation process used within the pharmaceutical industry but in modern time, granulation technology has been widely used by a wide range of industries, such as Pharmaceutical. "granulated" material is derived from the Latin word "granulatum," meaning grained [3, 4]. These industries employ agglomeration techniques to reduce dust, provide ease of handling, and enhance the material's ultimate utility. Granulation is process of particle designing [2]. Granulation is required to prevent segregation, to improve flow properties, to improve compaction [1].

Granulation is the process of collecting particles together by creating bonds between them. Bonds are formed by compression or by using a binding agent. If one were to make tablets from granulated sugar versus powdered sugar, for example, powdered sugar would be difficult to compress into a tablet and granulated sugar would be easy to compress [5]. Powdered sugar's small particles have poor flow and compression characteristics. These small particles would have to be compressed very slowly for a long period of time to make a worthwhile tablet. The granulation process combines one or more powders and forms a granule that will allow the tableting process to be predictable and will produce quality tablets within the required tableting speed range [6].

Granulation Mechanisms include wetting and nucleation, coalescence or growth, consolidation, and attrition or breakage. Initial wetting of the feed powder and existing granules by the binding fluid is strongly influenced by spray rate or fluid distribution as well as feed formulation properties, in comparison with mechanical mixing [7].

Granules are produced to enhance the uniformity of the API (active pharmaceutical ingredient) in the final product, to increase the density of the blend so that it occupies less volume per unit

weight for better storage, to facilitate metering or volumetric dispensing, to reduce toxic exposure and process-related hazards, and to improve the appearance of the product [2]. Consequently, the ideal characteristics of granules include spherical shape for improved flow, narrow particle size distribution for content uniformity and volumetric dispensing, sufficient fines to fill void spaces between granules for better compaction and compression characteristics, and adequate moisture and hardness to prevent breaking and dust formation during process [6]. For certain drugs that have non-concentration dependent pharmacodynamics, such as etalactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration [30].

The type of process selection requires thorough knowledge of physicochemical properties of the drug, excipients, required flow and release properties, etc. Granulation technologies like roller compaction, spray drying, supercritical fluid, low/high shear mixing, fluid bed granulation, extrusion/spheronization, etc. have been successful for many decades in the preparation of various pharmaceutical dosage forms. Pharmaceutical granulation technology continues to change, and various

improved, modified, and novel techniques and technologies have been made available along the course. The aim of this review is to give the reader a glimpse of the latest techniques and technologies with regard to pharmaceutical granulation. Subsequently, this review gives a short description about each development along with its significance and limitations.

Used Granulation Process

- A. Wet granulation that utilize a liquid in the process
- B. Dry granulation that requires no liquid.

The primary methods by which the agglomerated granules are formed include solid bridges, sintering, chemical reaction, crystallization and deposition of colloidal particles [3, 5].

The dry granulation process is used to form granules without using a liquid solution because the product to be granulated may be sensitive to moisture and heat. Wet granulation involves the massing of a mix of dry primary powder particles using a granulating fluid (the process of adding a liquid solution to powders). The fluid contains a solvent which must be volatile, so that it can be removed by drying, and be non-toxic

Table 1: Advantages of Wet granulation & Dry granulation with limitations

Method	Advantage	Limitations
Wet Granulation	<ul style="list-style-type: none"> * Robust process suitable for most compounds. * Imparts flow ability to a formulation. * Can reduce elasticity problems. * Coating surface with hydrophilic polymer can improve wettability. * Binds API with excipient, thus reducing segregation potential. 	<ul style="list-style-type: none"> * Expensive: time & energy consuming process. * specialized equipment required. * stability issues for moisture sensitive and thermolabile API with aqueous granulation.
Wet Granulation (non-aqueous)	<ul style="list-style-type: none"> * Suitable for moisture sensitive API * vacuum drying techniques can remove/ reduce the need for heat. 	<ul style="list-style-type: none"> * Expensive equipment. * Needs organic facility. * Solvent recovery issues. * Health and environment issues.
Dry Granulation (Slugging of roller compaction)	<ul style="list-style-type: none"> * Eliminates exposure to moisture and drying. 	<ul style="list-style-type: none"> * Dusty procedure. * Not suitable for all compounds. * Slow process.

The type of process selection requires thorough knowledge of physicochemical properties of the drug, excipients, required flow and release properties, etc. On the basis of those properties formation of granules process or technique might be different. Pharmaceutical granulation technology may improve this process that we found in recent progress in granulation process.

This review focuses on the recent progress in the granulation techniques and technologies such as pneumatic dry granulation reverse wet granulation, steam granulation, moisture-activated dry granulation, thermal adhesion granulation, freeze

granulation, and foamed binder or foam granulation. This review gives an overview of these with a short description about each development along with its significance and limitations.

Wet Granulation

Wet granulation involves the massing of a mix of dry primary powder particles using a granulating fluid. The granulating fluid contains a solvent that must be volatile, so that it can be removed by drying. Typical liquids include water, ethanol and isopropanol either alone or in combination [9].

Table 2: Merit and Demerits of Wet Granulation

Merits	Demerits
<ul style="list-style-type: none"> ➤ The cohesiveness and compressibility of powders are improved. ➤ Good distribution and uniform content ➤ A wide variety of powders can be possessed together in a single batch. ➤ Controlled release dosage form can be accomplished by the selection of a suitable binder and solvent. 	<ul style="list-style-type: none"> ➤ Because of large number of processing steps, it requires a large area with temperature and humidity. ➤ It requires a number of pieces of expensive equipment also time consuming. ➤ There is a possibility of material loss during processing due to transfer of materials from one unit to another and have possibility of cross contamination.

Conventional wet granulation involved low shear granulation, high shear granulation and fluid bed granulation.

A. Low shear granulation

It is the traditional method of making granules. Four

equipments are mainly used in this case:

1. 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

2. Planetary mixer to make the wet mass or paste
3. Oscillating granulator to make the wet granules
4. Dryer to dry the wet granules (Tray dryer or fluidized dryer)

Table 3: Low shear Granulation

Benefits	The process is not very sensitive to changes in the characteristics of the granules ingredients.
	The end point of the massing process can often be determined by inspection.
Disgrace	Multiple steps.
	Long duration.
	The need for several pieces of equipments.
	The high material loss that can be incurred because of transfer stages.

B. High shear mixture granulation

High shear mixture has been widely used in Pharmaceutical industries for blending and granulation. Blending and wet massing are accompanied by high mechanical agitation by an impeller and a chopper. Mixing, densification and agglomeration are achieved through shear and compaction force exerted by the impeller.

Table 4: High Shear Granulation

Benefits	➤ Short processing time.
	➤ Less amount of liquid binders required compared with fluid bed.
	➤ Highly cohesive material can be granulated.
Disgrace	➤ High-shear granulator produces less compressible granules when compared to low-shear granulator.
	➤ Over wetting of the granules may lead to formation of large sized lumps.
	➤ Thermolabile materials could be chemically degraded due to increase in temperature.

C. Fluid bed granulation

Fluidization is the operation by which fine solids are transformed into a fluid like state through contact with a gas. At a certain gas velocity, the fluid will support the particles giving them free mobility without entrapment. Fluid bed granulation is a process by which granules are produced in single equipment by spraying a binder solution onto a fluidized powder bed. The system involves the heating of air and then directing it through the material to be processed. Later, the same air exit through the voids of the product⁷. Fluid bed processing of pharmaceuticals was first reported by Wurster, by using air suspension technique to coat tablets later used this technique in granulating and drying of pharmaceuticals^[3,6], for the preparation of compressed tablets. Fluidized bed system contains various components such as-Air handling unit (AHU), Product container and air distribution, Spray Nozzle, Disengagement area and process filters, Exhaust blower or Fan, Control system and Solution delivery system.

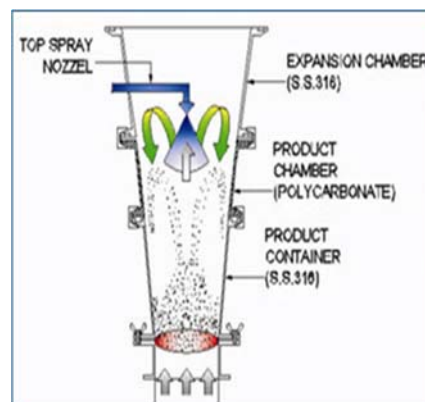


Fig 1: (Fluid Bed granulation)

Advantages

- Single unit system
- The process can be automated once the conditions affecting the granulation have been optimized.

Disadvantages

- Initially expensive and optimization of granulation needs extensive development work
- Fluidized bed systems may not provide adequate mixing of powder components. In fact there is a tendency for demising to occur when there are disparities in particle size or density in the materials being processed.
- Particles with granulating agent on their surface tend to stick to the equipment filters.

Recent progress in wet granulation

Wet granulation has witnessed various technical and technological innovations such as

- Reverse Wet Granulation.
- Steam Granulation
- Moisture-Activated Dry Granulation Or Moist Granulation,
- Thermal Adhesion Granulation,
- Melt Granulation,
- Freeze Granulation,
- Foamed Binder or Foam Granulation.

Reverse wet granulation

Reverse wet granulation process was developed and studied involving immersion of dry powder into the binder liquid, thus eliminating the traditional granule nucleation process. The reverse-phase process proceeds in the direction of reduced liquid saturation, thus decreasing the risk of uncontrolled growth and batch loss^[10].

It improves dissolution characteristics of poorly water soluble drugs by allowing uniform distribution of binder^[8, 10].

The primary mechanism of the reverse-phase granulation process was breakage of large moist agglomerates and mechanical dispersion of the binder liquid throughout the powder formulation. The size and porosity of reverse-phase granules are controlled by the liquid saturation and impeller speed, with these physical properties being best described by the dimension less Stokes deformation number and the growth regime map^[11].

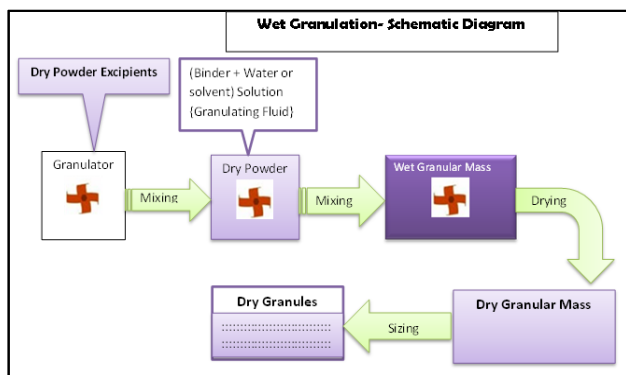


Fig 2: (Schematic diagram- Wet granulation)

Merits of Reverse Wet Granulation over Conventional Wet Granulation

- Improves the dissolution characteristics of the poorly water-soluble drugs by allowing uniform distribution of the binder. And also improved flow properties of powders.
- Increases the chances of adequate and uniform contact between the drug and hydrophilic polymer for better dissolution.
- Uniform wetting and erosion of the granules.

Steam Granulation

In steam granulation technique steam is used as a binder instead of water [12]. A steam granulation technique involves the injection of a jet of steam into a bed of fluidized particles to be granulated. The jet of steam is substantially enveloped by a jet of air to inhibit the premature condensation of the steam onto the fluidized particles and/or the condensation of the steam onto the neighboring walls of an apparatus employed to fluidize the particles, thereby this process inhibits excessive wetting and lumping of the particles during their granulation [13, 14].

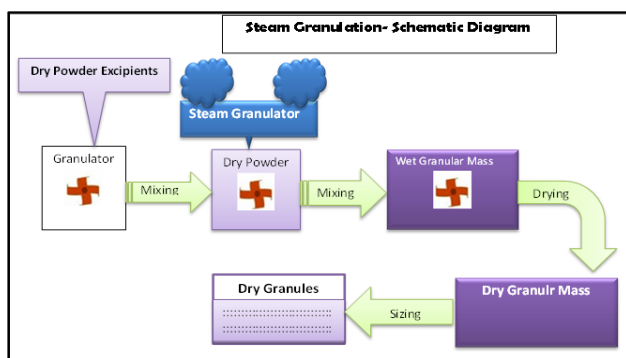


Fig 3: (Schematic diagram- Steam granulation)

Table 5: Merits and Demerits of Steam Granulation Process

Merits	Demerits
<ul style="list-style-type: none"> • Uniformly distributed in the powder particles. • Higher diffusion rate. • Results in more spherical granule formation. • No health hazards. • Maintain sterility 	<ul style="list-style-type: none"> • Requires special equipment for steam generation and transportation. • Requires high energy inputs. • Thermo labile materials are poor candidates. • More safety measure required. • Not suitable for all the binders

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 [15]. Then, any excess moisture is absorbed by the addition of a moisture-absorbing substance. Moist granulation yielded an increase in particle size compared to direct compression; these results are comparable to those from the traditional wet granulation after drying and screening. Based only on the particle size, moist granulation appears comparable to conventional wet granulation for this formula. The moist granulation technique appears to have potential for the development of controlled-release formulations [15, 18].

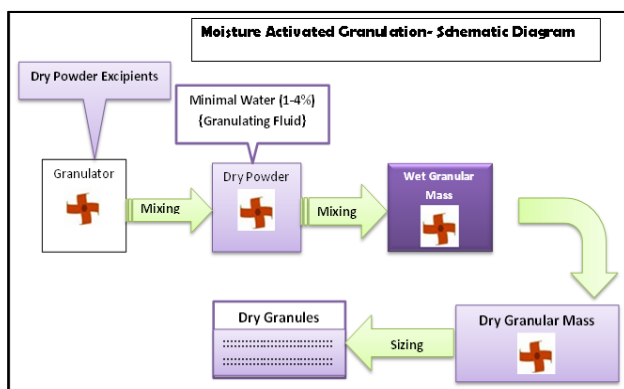


Fig 4: (Schematic diagram- Moisture activated granulation)

In MADG moisture is used to activate granule formation, without the need to apply heat to dry the granules. MADG is suitable for continuous processing. There are two main stages in MADG [16]:

- ✓ Agglomeration
- ✓ Moisture distribution/ Absorption

Table 6: Moisture activated Granulation [17, 18]

Benefits	➤ Applicable to more than 90% of the granulation need for pharmaceutical, food and nutritional industry.
	➤ Time efficient.
	➤ Suitable for continuous processing.
Drawbacks	➤ Less energy involve during processing.
	➤ Moisture sensitive and high moisture absorbing APIs are poor candidates.

Thermal Adhesion Granulation (TAG)

It's analogous to moist granulation and utilizes addition of a small amount of granulation liquid and heat for agglomeration. This process uses both water and solvent as granulation liquid. In addition to this, heat is used to facilitate the granulation process.

Drug & excipient mixture is heated to a temperature of 30-130° C in a closed system under tumble rotation to facilitate the agglomeration of the powder particle [19].

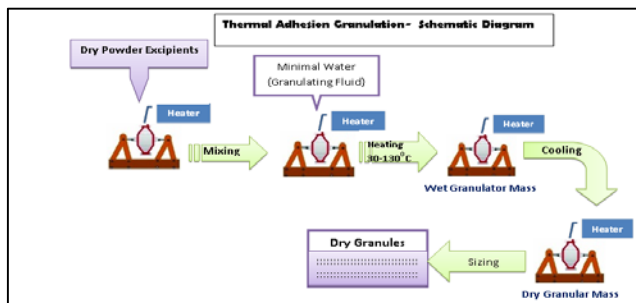


Fig 5: (Schematic diagram- Thermal Adhesion Granulation)

This technique eliminates the drying process due to the addition of low amount of granulation liquid, which is mostly consumed by the powder particles during agglomeration. Granules of the required particle size can be obtained after cooling and sieving. It is applicable for preparing direct tableting formulations [19, 20].

Melt granulation

Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a melttable binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation²¹. Melt granulation is an appropriate alternative to other wet granulation techniques which are used for water sensitive materials.

Melt granulation process is currently applied in the pharmaceutical for the manufacture of variety of dosage forms and formulation such as immediate release and sustained release pellets, granules and tablets [22, 23].

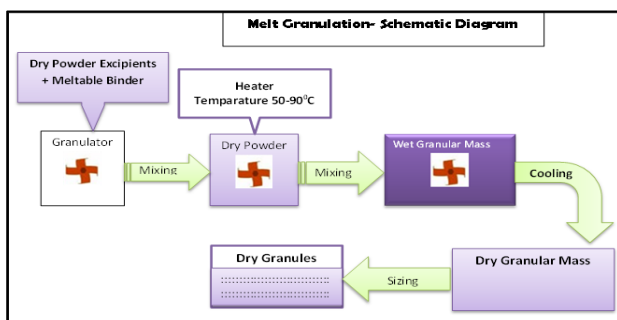


Fig 6: (Schematic diagram- Melt granulation)

Table 7: Melt Granulation

Advantage	Disadvantage
<ul style="list-style-type: none"> ➤ Time and cost effective. ➤ Controlling and modifying the release of drugs. ➤ Water sensitive drugs are good candidates. 	<ul style="list-style-type: none"> ➤ Heat sensitive materials are poor candidates. ➤ Lower melting point binder may melt/ soften during handling or storage.

Freeze Granulation

Freeze granulation technology involves spraying droplets of a liquid slurry or suspension into liquid nitrogen followed by freeze-drying of the frozen droplets. By spraying a powder suspension into liquid nitrogen, the drops are instantly frozen into granules, and in the subsequent freeze drying process, the granules are dried by sublimation of ice without any

segregation effects [24, 25].

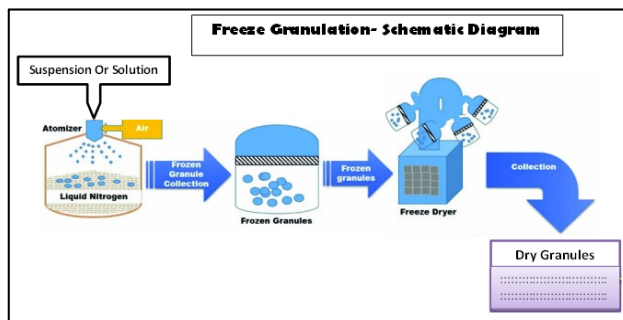


Fig 7: (Schematic Diagram- Freeze granulation)

Advantages

- Able to control the granule density through the solid content of the suspension, preparation of granules with no cavities
- Useful for the preparation of granules that needs to be prepared from suspensions whose particle size and homogeneity need to be preserved.
- Minimize damage of organic compounds and improve stability and/or solubility.
- High product yield due to low waste of material
- Possibility of recycling organic solvents.

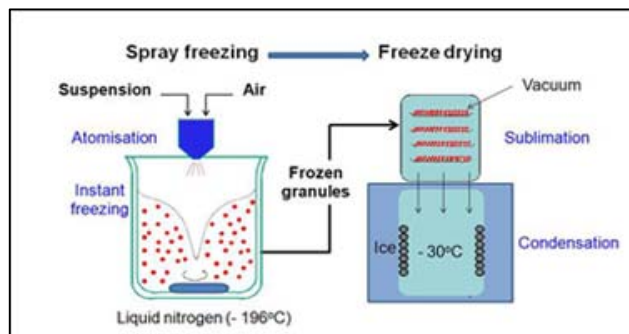


Fig 8: (Schematic diagram- Freeze drying)

Foam Granulation

Involves the addition of liquid/aqueous binder as foam instead of spraying or pouring liquid onto the powder particles. No spraying nozzle is used, less water required and cost effective. A simple foam generation apparatus is used to incorporate air into a conventional water soluble polymeric excipients binder such as METHOCEL [26, 27].

Advantages

1. No spray nozzle is used
2. Improve process robustness
3. Less water required for granulation
4. Time efficient drying
5. Cost effective
6. Uniform distribution of binder
7. No over wetting
8. Applicable for water sensitive formulation.

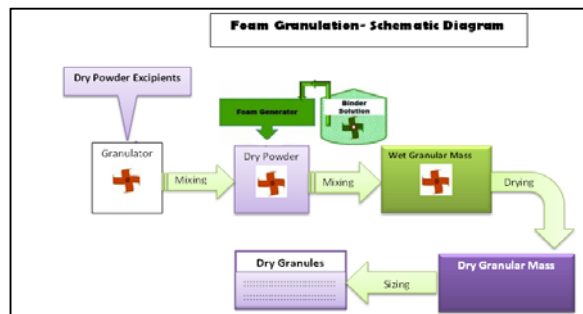


Fig 9: (Schematic diagram- Foam granulation)

Dry Granulation

Dry granulation is a simple and low cost method and becoming more popular because of its simplicity and cost efficiency. Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents [31]. In dry granulation method the primary powder particles are aggregated at high pressure. There are two main processes – either a large tablet (known as slug) is produced in a heavy duty tableting press(known as slugging) or the powder is squeezed between two rollers to produce a sheet of material (roller compaction) [9]. The two different types are illustrated in below:

Slugging process

Granulation by slugging is the process of compressing dry powder of tablet formulation with tablet press having die cavity large enough in diameter to fill quickly. The accuracy or condition of slug is not too important. Only sufficient pressure to compact the powder into uniform slugs should be used. Once slugs are produced they are reduced to appropriate granule size for final compression by screening and milling [9].

Factors which determine how well a material may slug

- i) Compressibility or cohesiveness of the matter
- ii) Compression ratio of powder
- iii) Density of the powder

- iv) Machine type
- v) Punch and die size
- vi) Slug thickness
- vii) Speed of compression
- viii) Pressure used to produce slug

Roller compaction

The compaction of powder by means 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 for production into granules.

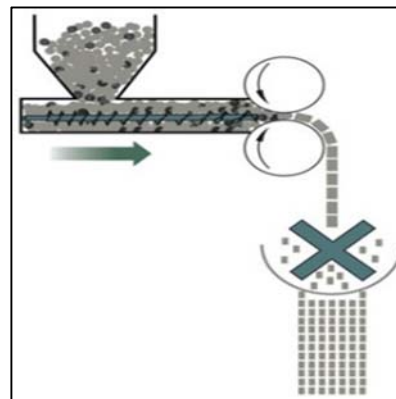


Fig 10: (Roller compaction in dry granulation)

Steps involved in dry granulation process are-

- I. Milling of drugs and excipients
- II. Mixing of milled powders
- III. Compression into large, hard tablets to make slug
- IV. Screening of slugs
- V. Mixing with lubricant and disintegrating agent
- VI. Tablet compression

Table 8: Dry Granulation

Advantage	This is also called double compression or slugging method, this is valuable alternative to direct compression, where the dose of drug is too high or to wet granulation when the drug is sensitive to heat, moisture or both. This method is also used when other methods of granulation yield granules with poor flow or compression properties, because there are less chances of segregation of drug and excipients.
Disadvantage	Long processing time, a relatively high capital investment on heavy duty presses or compactors.

Recent progress in dry granulation

Dry granulation could be achieved either by roller compaction or by slugging. There has not been much progress in the dry granulation technique and technology in comparison to wet granulation, except for one important innovation known as pneumatic dry granulation technology developed by Atacama Labs Oy (Helsinki, Finland), which is described below [28].

Pneumatic Dry Granulation (PDG)

The pneumatic dry granulation process is a new and patent-pending technology. The granulation process is based on the use of roller compaction with very low compaction force together with a proprietary air classification method. The method enables production of granules with extraordinary combination of flow ability and compressibility [28, 29].

PDG technology can achieve,

- ✓ High drug loading, even with difficult APIs and

- combinations
- ✓ Taste masking
- ✓ Excellent stability

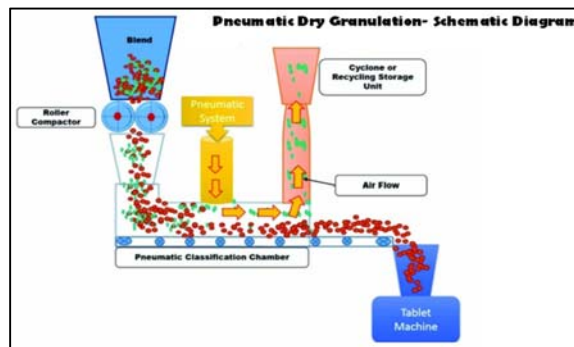


Fig 11: (Diagram of Pneumatic Dry Granulation)

Merits of Pneumatic Dry Granulation

- Faster speed of manufacturing compared with wet granulation.
- Lower cost of manufacturing compared with wet granulation.
- The system is closed offering safety advantages due to low dust levels and potential for sterile production or handling of toxic materials,
- The end products are very stable - shelf life may be enhanced,
- Little or no waste of material,
- Scale-up is straightforward,
- The granules and tablets produced show fast disintegration properties, offering the potential for fast release dosage forms, and
- Release time can be tailored to requirements.

Table 9: Summary of recent progresses in granulation techniques and technologies

Techniques/ Technologies	Description	Granule Characteristics	Merits	Limitations	Equipment
Pneumatic Dry Granulation	*Dry granulation. *Mild Compaction and Pneumatic classification	*Porous, highly compressible. *Taste making. *Fast disintegration. *Release time modification.	*Drug loading. *Thermolabile and moisture sensitive drugs. *Product stability. *Cost and waste	*Recycled granule quality. *Segregation potential. *Friability.	*Roller compaction with air steam or vaccum.
Reverse Wet Granulation	*Wet granulation *Water or solvent is granulating liquid	*Uniform wetting. *Uniform erosion.	*Particle size *Spherical shape *Poorly water soluble drugs	*Larger particle size *Lower porosity. *Many problem similar to conventional wet granulation.	*High speed mixer.
Steam Granulation	*Wet granulation. *Steam is granulating liquid.	*Diffusionate. *Uniform distribution. *Surface area. *Spherical shape.	*Eco-friendly *sterility process time *No solvent use *No health hazards.	*local over heating/wetting. *High energy inputs. *Thermolabile drugs. *Limited binders	*High speed mixer with steam generator regulator
Moist-Activated Dry Granulation	*Wet granulation. *1-4% water is granulating liquid and moisture-absorbing material	*Uniform size. *Flowability. *Compressibility.	*Less energy input. *No drying process *Wide applicability *Continuous processing. *Shorter process time *Process variables	*Moisture sensitive drugs *Impossible high drug loading. *Limited absorbents.	*High-shear mixer coupled with a sprayer.
Thermal adhesion Granulation	*Wet granulation. *Low water solvent is granulating liquid and heating at 30-130°C	*Flowability. *Friability. *Tensile Strength.	*Drug loading *No drying process dust	*High energy inputs. *Thermolabile and moisture sensitive drugs. *Limited binders	*Tumble blender or similar equipment coupled with heating system.
Melt Granulation	*Wet granulation. *Meltable binder as granulating liquid, heating at 50-90°C	*Possible modified release. *Dissolution.	*No water or solvent *No drying process *Energy input *Cost and process time *water sensitive drugs.	*Thermolabile drugs. *Limited binders	*High shear mixer. *Fluidized be
Freeze Granulation	*Wet granulation. *Spray freezing and subsequent freeze drying for slurry or suspension.	*Uniform size. *Flowability. *Spherical shape.	*Granule homogeneity *Thermolabile drugs *Granule density control *Material waste	*limited solvent medium. *Only suitable for conversion of liquid slurry or suspension to granules.	*Spray freezer coupled with freeze dryer.
Foam Granulation	*Wet granulation. *Foam as granulating liquid.	*Uniform binder distribution. *No over wetting.	*water requirement. *No spray nozzle use *Low water required. *Cost & process time *Water sensitive drugs.	*Moisture sensitive drugs. *Limited binders.	*High shear mixer or fluidized bed granulator coupled with foam generator regulator.

Conclusion

Technical and technological progress that helps in development and ease other facilities is always desirable. Obviously, the pharmaceutical granulation techniques and technologies have improved over the years. Nevertheless, efficient and cost-effective manufacturing methods have always been the keen interest of the pharmaceutical industries which helps them in research and development progress globally.

During the formulation development, each drug substance poses a unique challenge that must be taken into consideration at the process selection stage by the formulation development scientists. Each technique has its own merits and limitations, and the type of technique and technology selection requires thorough knowledge of physicochemical properties of the drug, excipients, required flow and release properties, etc. in addition to the granulation techniques and technologies itself. This review discussed the recent developments in granulation technology for conventional release dosage formulations only.

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