Review Article

Advanced Granulation Technology

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ABSTRACT

Granulation is one of the most important unit operations in production of pharmaceutical oral dosage form. Granulation is defined as the size enlargement process in which fine and smaller particle are aggregated to form strong and stable particles called granules. Granulation

Process will improve flow and compression characteristics, reduce segregation, improve content uniformity, and eliminate excessive amounts of fine particles. The results will be improved yields, reduced tablet defects, increased productivity, and reduced down time. A pharmaceutical organization employs different techniques such as direct compressing, wet-granulation, or dry granulation methods for the production of pharmaceutical products. The method of selection depends on the ingredients individual characteristics and ability to properly flow, compresses, eject, and disintegrate. The present review mainly focused on advanced granulation techniques.

Keywords: Granulation, Pharmaceutical dosage forms, improved yields. Pneumatic Dry Granulation, Freeze granulation, Moisture activated dry granulation, Foam granulation, Steam granulation, Thermal Adhesion Granulation.

INTRODUCTION

Granulation is one of the most significant unit operation in the production of pharmaceutical solid oral dosage forms. Granulation is the process in which primary powder particles are made to adhere to form larger, multi particle aggregates called granules**.** Pharmaceutical granules usually made in the size range of from 0.2 to 4.0 mm, depending on their subsequent application. After granulation process, the granules will either be packed (when used as a dosage form, example: Powder form), or they may be mixed with other excipients prior to tablet compression or capsule filling. Granulation is mainly used to improve the flow properties of powders and compressibility of powders, and to prevent segregation of blend components. Granulation method can be broadly classified in to 3 types

1. Wet granulation, 2.Dry granulation 3. Granulation incorporating bound moisture

REASONS FOR GRANULATION

To improve the compaction characteristic of the mix..

- ✓ To improve the flow properties of the mix.
- ✓ To prevent the segregation of the constituents of the powder mix.
- ✓ Granules being denser than the powder mix, occupies less volume per unit weight. They are more convenient for storage and shipment.
- ✓ Materials which are slightly hygroscopic may adhere and form a cake if stored as powder. Granulation may reduce this hazard as the granules will absorb some moisture and yet retains their flowability because of their size.

IDEAL CHARACTERISTICS OF GRANULES

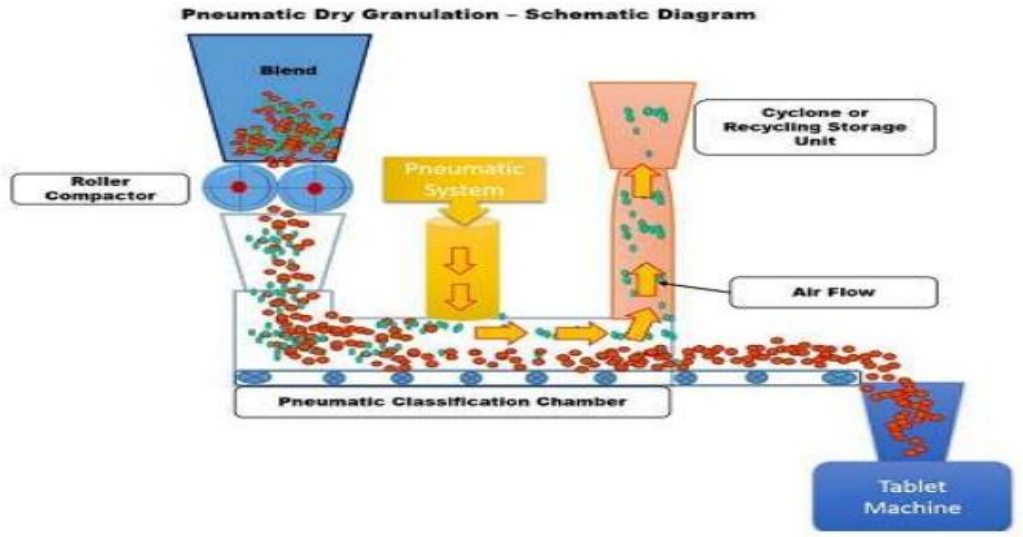
The ideal characteristics of granules include spherical shape ,smaller particle size distribution with sufficient fines to fill void spaces between granules, adequate moisture (between 1-2%), good flow, good compressibility and sufficient hardness.

RECENT ADVANCES IN GRANULATION TECHNOLOGIES ARE

1) Pneumatic Dry Granulation (PDG)

The PDG Technology:

- ✓ It can produce porous granules with excellent compressibility and flowability properties.
- ✓ It works on the basis of pneumatic dry granulation principle, a novel dry method for automatic or semiautomatic production of granules,
- ✓ It enables flexible modification of processing variables such as drug load, disintegration time and tablet hardness.



- **It Is possible to achieve**
- Incorporation of high dose drugs, even with‘ difficult’ APIs and combination formulas.
- Taste masking.
- Excellent stability.
- It is compatible with other techniques, such as sustained release, fast release, etc.
- It is the matter of more number of patent applications and
- It is suitable for thermo sensitive and moisture.

GRANULATION

The pneumatic dry granulation process can granulate virtually any pharmaceutical solid dosage ingredient. The granulated material has exceptionally good flowability, and compressibility properties. PDG Technology has been used with superior results in developing fast-release, controlled-release, fixed-dose,and orally disintegrating tablets. The technology is applicable to practically any solid dosage pharmaceutical product.

Pneumatic Dry Granulation Replaces Wet Granulation

Today, wet granulation is the most commonly used granulation method. Formulation teams will usually target a direct compression or dry granulation formulation where possible but in approximately 80% of the cases they end up with a wet granulation formulation due to processing issues.

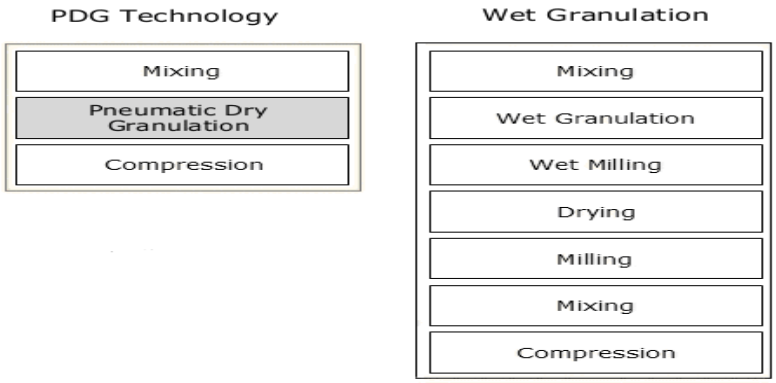


Fig. 1: PDG Technology and wet granulation comparison

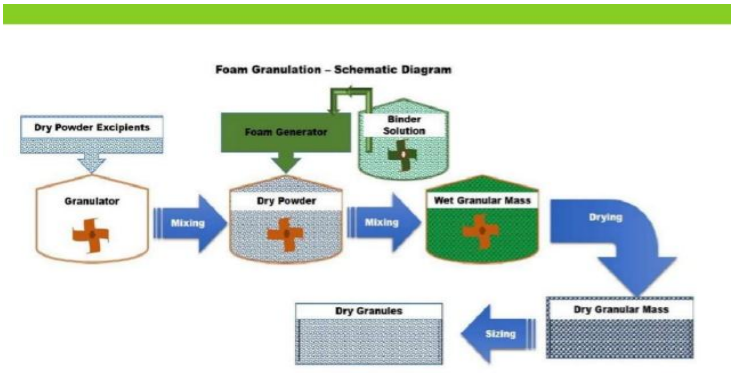
Wet granulation is also unsuitable for moisture sensitive and heat sensitive drugs, it is more expensive than dry granulation, it is relatively labour intensive and can take a long time. There are a large number of process steps and each step requires qualification, cleaning, and cleaning
validation, high material losses can be incurred because of the transfer between stages, there is the need for long drying times. Scale up is usually an issue, and there are considerable capital requirements. PDG Technology solves the above problems. PDG Technology granules have excellent properties compared to wet granulation, dry granulation and direct compression. At the same time, the granules show both high compressibility and flowability. The results can
be archived without using exotic and expensive excipients.

Advantages of PDG Technology

The PDG Technology has a number of advantages

- ✓ Good granulation results even at high drug loading have been achieved even with material known to be historically difficult to handle.
- ✓ 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.

2) FOAM BINDER TECHNOLOGY



Foam binder technology for the development of novel foamed binder technology deserves for The DowChemical Company can help to achieve faster,simpler, and safer wet granulation processing.The formulation scientists of Dow Chemical Company have proven the binder distribution in the formulation

material using METHOCEL polymers and resulted with excellent processing advantages. When compared to traditional spray processing, this novel technology offers shorten processing times by reducing water requirements. It can speed up granulation processing and improve reproducibility through more uniform binder distribution. Inspite of that, it avoids usage of spray nozzles and their many variables in granulation processing equipment. Foam processing also offers better end point determinations and reduced equipment clean-up time. Foamed binder processing offers many key advantages, doesn't demand new equipment or radical changes in processing techniques. It can very easily use it with familiar high shear, low shear, or fluid bed granulation equipment, in both laboratory and large-scale production. handling of potent drug .compounds.

HOW THE FOAM BINDER WORKS

Foam granulation takes advantage of the tremendous increase in the liquid surface area and volume of polymeric binder foams to improve the distribution of the water/binder system throughout the powder bed of a solid dose pharmaceutical formulation. A simple foam generation apparatus is used to incorporate air into a conventional water-soluble polymeric excipients binder such as METHOCEL hypromellose (hydroxypropyl methylcellulose). The resulting foam has a consistency like shaving cream. Hypromellose polymers are ideal candidates for this technology because they are excellent film formers and create exceptionally stable foams. In a small-scale laboratory setting or in a full-scale production setting, the foam generator can be connected directly to high-shear, low-shear, or fluid bed granulation equipment.

Extremely efficient binder delivery and particle coverage

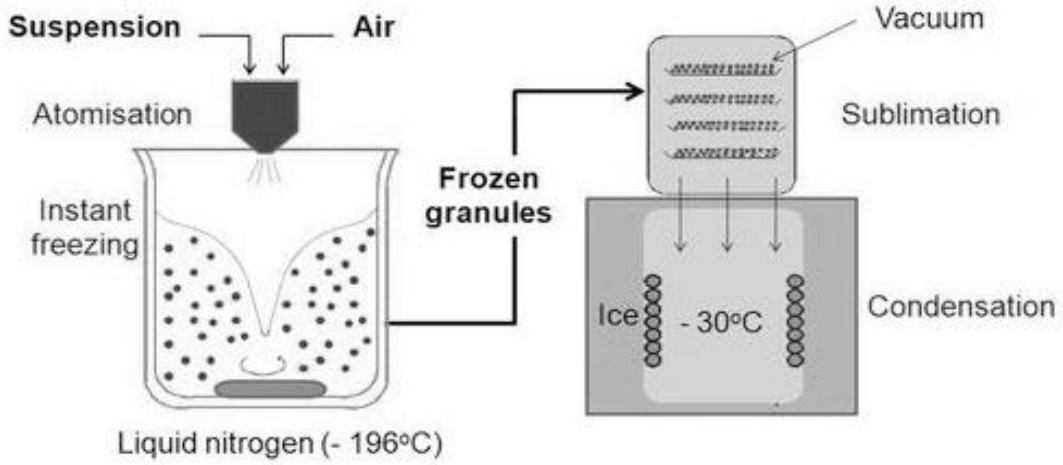
The key to the effectiveness of foam binder performance is rapid and extremely efficient particle coverage. Compared to sprayed liquid binders, foamed binders offer much higher surface area, and they spread very rapidly and evenly over powder surfaces. The foamed binders and the powder particles show excellent mutual flow through one another. The foam binder also shows a low soak: spread ratio, so particle surfaces are quickly and completely covered. By contrast, spraying is a cumulative process that begins with small liquid droplets "dappling" particle surfaces
until enough binder liquid accumulates to initiate particle agglomeration. Spraying requires considerably more water and processing time than a foamed binder to achieve particle agglomeration. The foam binder technology also eliminates the need for spray nozzles and all of their attendant variables, such as nozzle configuration, distance from the moving powder bed, spray patterns, clogging, droplet size, and droplet distribution. The dilute binder solutions are easy to handle in processing. Overall, foam binder processing is easier, faster, and allows safer
handling of potent drug compounds.

Fig.: Foamed Binder

3) Freeze Granulation Technology

The credentials for development of this novel alternate technique reserves for Swedish Ceramic
Institute (SCI).This type of granulation enables production of dry granules from suspension. Here the mechanism of granulation includes powder suspension is sprayed into liquid nitrogen and the drops

(granules) are instantaneously frozen. Subsequently the granules are dried by sublimation of the ice without any segregation effects as in the case of traditional drying in air.



The resulting granules will be spherical free flowing with optimal homogeneity. In spite of high degree of homogeneity freeze granulation offers several advantages:

- It regulates the density of granules by the solid content of the suspension.
- Serious oxidation of non-oxides and metals are prevented as there is mild drying.
- No cavities in the granules.
- Very high yield of material is obtained.
- Possibility of recycling of organic solvents.
- Easy to clean the equipment.
- Reproducibility in production small (50-100 ml suspension) and large quantities of granules.

4)Melt Granulation Technology:

This technology is also called as thermoplastic cgranulation or melt agglomeration as the granules are obtained by the addition of either a molten binder or solid binder which melts during the process.

Principle: The process of granulation consists of combination of three phases:

I. Wetting and nucleation
II. Coalescence step
III. Attrition and breakage.

Wetting and nucleation step

• During the nucleation step the binder comes into contact with the powder bed and some liquid bridges are formed, leading to the formation of small agglomerates.

Two nucleation mechanisms are proposed by Schafer and Mathiesen.

I. Immersion
II. Distribution

Immersion

When the size of molten binder droplets is greater than that of fine solid particles, it leads to nucleation.

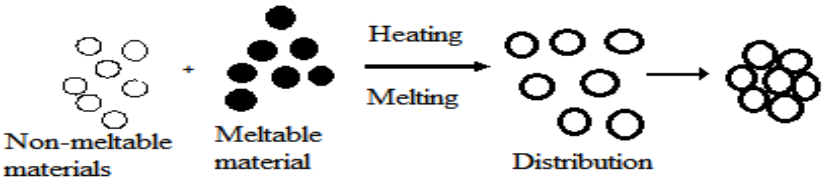
This process proceeds by depositing fine solid particles onto the surfaces of molten binder droplets.

Distribution

The molten binding liquid is distributed onto the surfaces of fine solid particles.

The collision of the wetted particles leads to nuclei formation.

Smaller the binder droplet size, low binder viscosity and high shearing forces are favorable conditions for nucleation by distribution method.



Coalescence steps

It involves the nuclei that have residual surface liquid to promote successful fusion of nuclei.

Plasticity to the nuclei is imparted to the surface liquid which is necessary for the deformation of nuclei surface for coalescence as well as promoting
the rounding of granulation.

Attrition- breakage step

This is the phenomenon of granulation fragmentation in that are solidified by tray cooling
to ambient temperature without the need for drying by a tumbling process.

Breakage plays an essential role by affecting the properties of melt granulation during the granulation phase.

Requirements of melt granulation

10-30% w/w of meltable binder with respect to that of fine particles is generally used.

Meltable binder used in this has a melting point within a range of 50-100°C.

For immediate release dosage forms, hydrophilic molecules are used while for prolonged release dosage forms, hydrophobic molecules are used Melting point of fine particles used should be at least 20°C higher than that of the maximum processing temperature.

Requirements for meltable binders

It should be solid at room temperature and has melting point ranging from 10 and 80°C.

These binders should be physically and chemically stable.

HLB should ensure the correct release of active substance.

There are two types of meltable binders:-

Hydrophilic meltable binders

Hydrophobic meltable binders

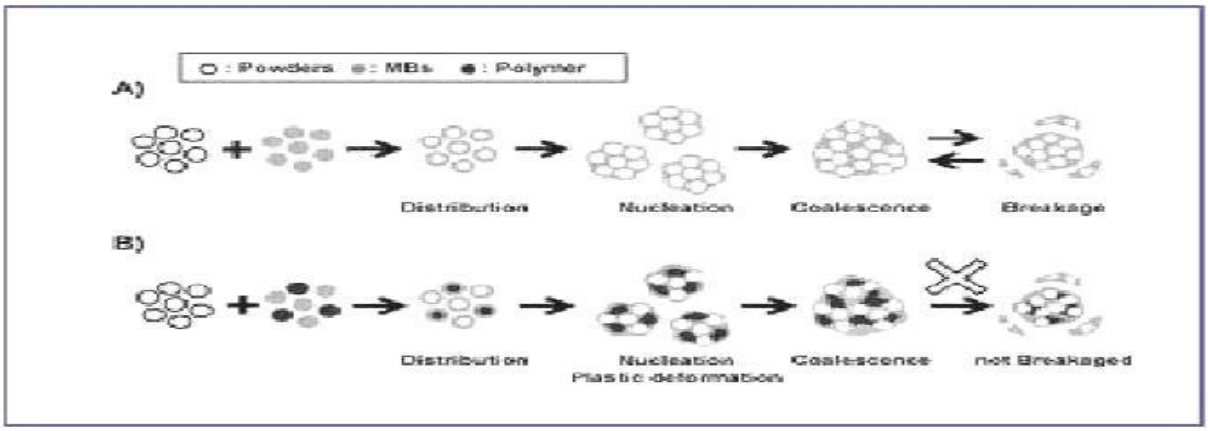


Fig. 4: Modes of distribution

Ideal characteristics of Meltable binders

1. Meltable binders should be solid at room temperature and the melting point should lie between 40 to 60° C.
2. The HLB value of the binder should ensure correct release of the active ingredient.

Advantages

No solvent is used and the processing steps needed are fewer thereby eliminating the time consuming drying steps.

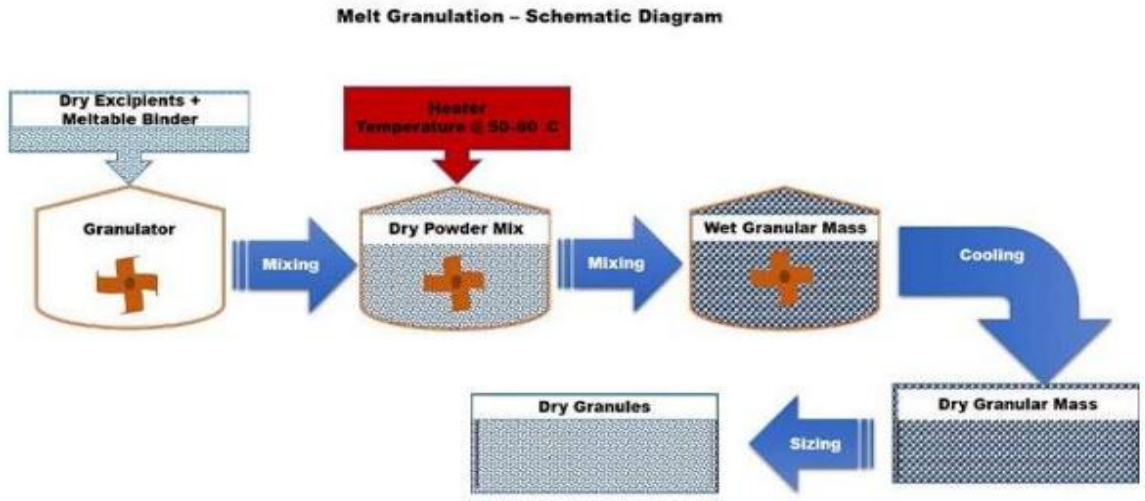
There is uniform dispersion of fine particles and it offers good stability at varying pH and moisture.

They can be applied safely in humans due to their non swellable and water insoluble nature .

Table 1: List of Binders.

Hydrophilic meltable binders generally used in the melt granulation technique.

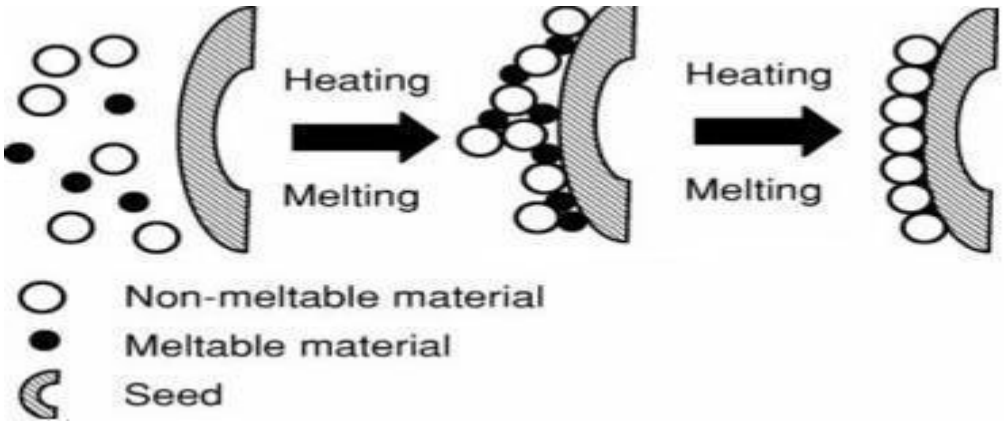
	Hydrophilic Meltable Binder Typical Melting Range (°C)
Gelucire	50/13 44-50
Poloxamer	188 50.9
Polyethylene glycols :	
PEG 2000	42-53
PEG 3000	48-63
PEG 6000	49-63
PEG 8000	54-63



5) Steam granulation *:* It is modification of wet granulation. Here steam is used as a binder instead of water.

• In this method of granulating particles involves the injection of the required amount of liquid in the form of steam.

• This steam injection method, which employs steam at a temperature of about 150° C., tends to produce local overheating and excessive wetting of the particles in the vicinity of the steam nozzles, there by causing the formation of lumps in the granulated product.



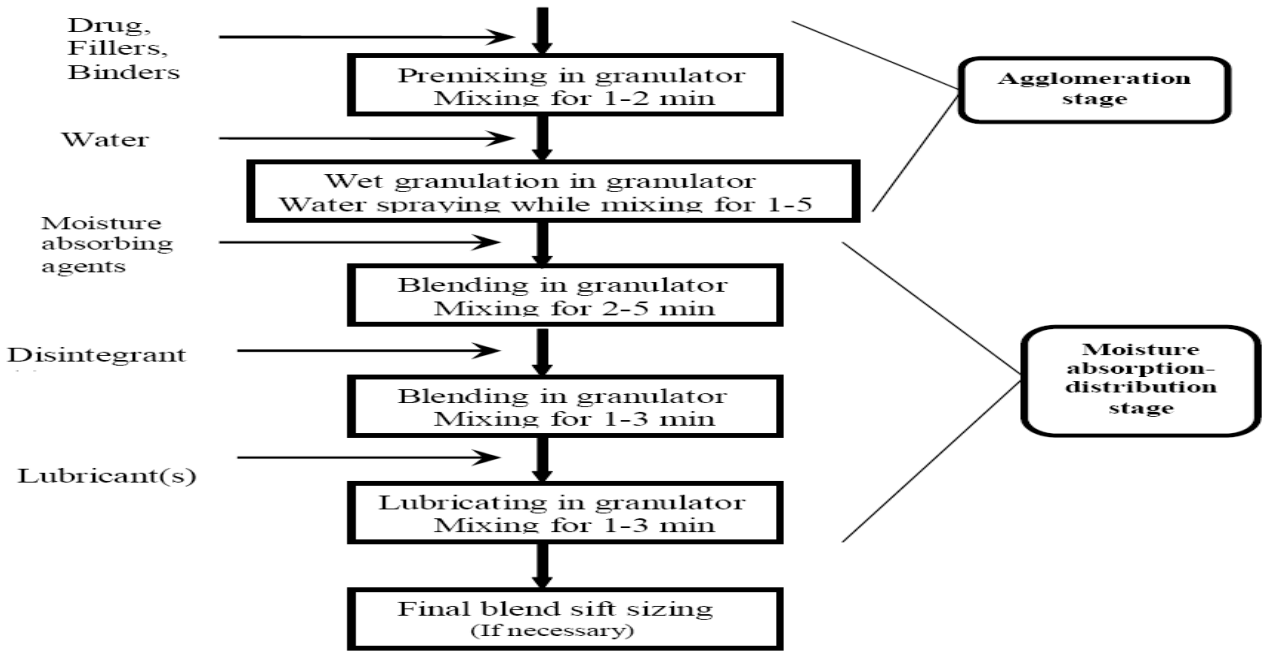
Advantages

_ Higher distribution uniformity,
_ Higher diffusion rate into powders,
_ Steam granules are more spherical
_ Have large surface area hence increased dissolution rate of the drug from granules,
_ Processing time is shorter therefore more number of tablets are produced per batch,
_ Compared to the use of organic solvent water vapor is environmentally friendly,

6. Moisture Activated Dry Granulation (MADG)

• In this method moisture is used to activate the granules formation but the granules drying step is not necessary due to moisture absorbing material such as MCC.
• The moisture-activated dry granulation process consists of two steps, wet agglomeration of the powder mixture followed by moisture absorption stages.
• A small amount of water (1–4%) is added first to agglomerate the mixture of the API, a binder, and excipients. Moisture absorbing material such as MCC and potato starch is then added to absorb any excessive moisture.

Fig.: Flow diagram of moisture activated dry granulation process.



After mixing with a lubricant, the resulting mixture can then be compressed directly into tablets. Hence, this process offers the advantage of wet granulation is that eliminates the need for a drying step.
• MCC, potato starch, or a mixture of 50% of each was used as moisture absorbing material.FMC Biopolymer has introduced two new excipient products to the Pharma market: Avicel HFE-102 and Avicel PH-200 LM, which are based on already existing excipients but have been generated to produce a different entity with improved benefits . Avicel PH-200 LM, based on microcrystalline cellulose (MCC), has been formulated to reduce the amount of water added to the granulation process Avicel PH-200 LM is a step up from FMC Biopolymer's Avicel PH-200
which had a moisture level of five per cent. The new product has a moisture level of no more than 1.5 per cent and can absorb approximately three to four times as much water from the granule. This advantage, along with enabling the use of MADG, meant the use of Avicel PH-
200 LM could eliminate the extra steps of milling, drying and screening, thereby reducing manufacturing costs and energy used. The process also produced larger particle size for optimal flow. This increases efficiencies to the manufacturing process. It takes aspects of wet granulation but eliminates the drawbacks of it. Also be useful for the use of active pharmaceutical ingredients (APIs) which were sensitive to moisture. Avicel HFE-102 is a new, proprietary co-spray dried MCC/mannitol high functionality binding excipient for direct compression. The co-spray drying added extra benefits to the excipient as it changed its properties combining the high compressibility of MCC and the low lubricant sensitivity of Mannitol.
The outcome was a harder, less friable and faster disintegrating tablet.

Advantage
- It utilizes very little granulating fluid.
- It decreases drying time and produces granules with excellent flow ability.
- Single production equipment (high shear granulator)
- No equipment change
- Lower tablet capping

No over and under granulation.

7. Granulex® Technology
The Granurex® precisely and consistently performs both coating and powder layering processes. In the pictures to the right, multiple coating and powder (ingredient) layers
demonstrate the accuracy and control of a Granurex® rotor processor, including the creation of the nonpareil.

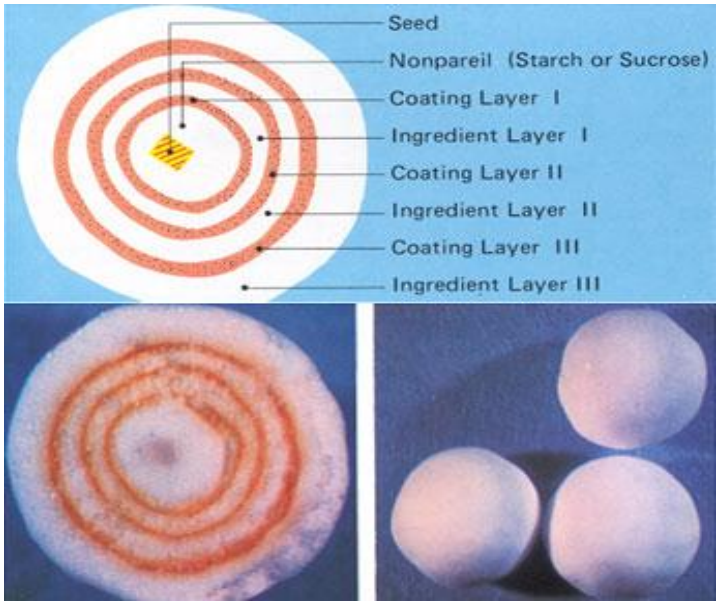


Fig.: Granurex® Technology: Precision coating and powder layering Processes.

Key feature

Unique, efficient granulation processes

Granules produced by the Granurex® are dense and spherical in shape. The Vector Corporation demonstrated that the Granurex® processes of Ciprofloxacin from a 7 µm poorly flowing powder to 200 µm granules with excellent flow characteristics.

One pot processing: A patented feature of the granulator Granurex® (Figure) is having unique ability to dry product within the same processing chamber. This unique drying method, combined with 12 bar construction, provides a true one-pot system, ideal for manufacturing highly potent and expensive pharmaceutical compounds.

Fig.: Onepot processing.

Increased batch capacities: In comparison to traditional rotor processors, the patented conical rotor plate (Figure) has tremendous capacity in increasing the batch capacity. The designed machine contains the product within the processing area and the peripheral spray guns are embedded into the product, which provides accurate coating with minimal spraying effect.

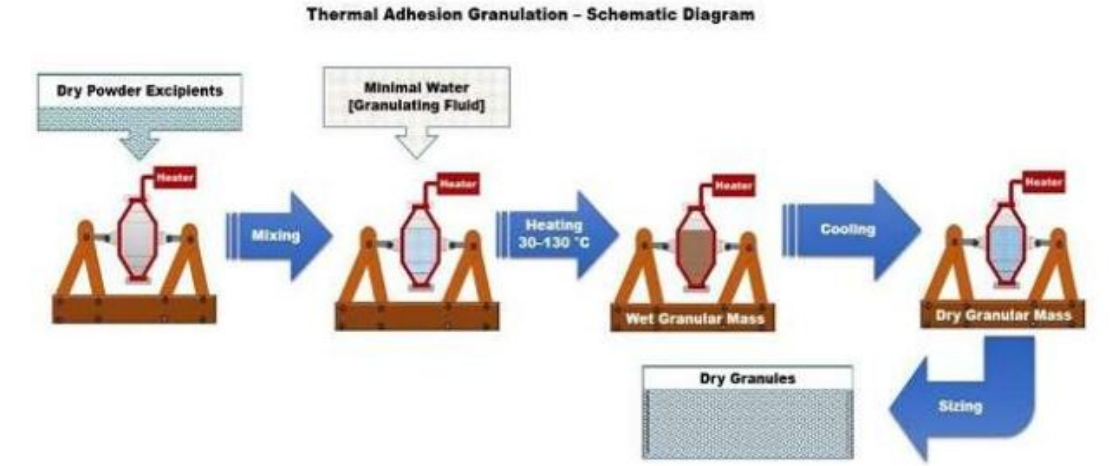
Fig.: Increased batch capacities

Maximum process flexibility: The Corporation has demonstrated maximum process flexibility using micronized acetaminophen as the base material; the Granurex® produced both a 100 µm granulation and a 200 µm spherical bead. In both of the examples, the acetaminophen core material had the same initial Mean Particle Size (X50) of 40 µm.. ..

8. Thermal Adhesion Granulation Process (TAGP)

It is applicable for preparing direct tabletting formulations. TAGP is performed under low moisture content or low content of pharmaceutically acceptable solvent by subjecting a mixture containing one or more diluents and/or active ingredients; a binder; and optionally a disintegrant to heating at a temperature in the range from about 30ºC to about 130ºC in a closed system under mixing by tumble rotation until the formation of granules. This method utilizes less water or solvent than traditional wet granulation method

31, 32 It provides granules with good flow properties and binding capacity to form tablets of low friability, adequate hardness and have a high uptake capacity for active substances whose tabletting is poor.
In this process, granules are formed during the moist powder under continuous tumble rotation, as the heated powder mass flows with in the container and agglomerates with the aid of the binder. Drying and milling to form the desired granules are unnecessary in the present invention due to the low amount of moisture introduced to the tableting mixture.
Another major advantage of granulating pharmaceutical products in a closed system is that it helps to minimize the generation of dust during powder processing. This technique serves to contain fine-powder active ingredients whose spread or loss from the system is not desirable due to their cost or biological activity.



9. Spheronization

Spheronization also known as Marumerization.The credentials for development of this technique reserved for Caleva Process Solutions Ltd, UK. It is the process where pellets (size from about 0.5 to 2.0 mm) are produced from mixtures of solids and liquids by the involvement of forming and shaping forces. During this process, extrudates are shaped into rounded or spherical granules. This process was first reported by Reynolds and by Conine and Hadley in 1970.

Advantages of spheronisation relevant to pharmaceutical industries

• Easy to coat.
• Separation of incompatible drugs.
• Ability to mix pellets with different release rates.
• Reduced risk of dose dumping.
• Reduced risk of local irritation in the gastro-intestinal tract.
• Less variable bio-availability. Particles of 1mm or less behave more like liquids in terms of gastric emptying
• Even distribution over the gastro-intestinal tract.

Process

Mixing

The ingredients are generally mixed in either a high-shear granulator or a more simple planetary mixer.

Extrusion

The extrusion of the materials is a necessary step prior to spheronization. The size of the spheres is governed by the diameter of the extrudate used for the spheronization process. In a spheronizer, it is possible to obtain spheres with a diameter ranging from about 0.5 mm to 2 mm.

Spheronisation

The ongoing action of particles colliding with the wall and being thrown back to the inside of the plate creates a "rope-like" movement of product along the bowl wall. The continuous collisions of the particles with the wall and with the friction plate gradually turn the cylindrical segments into spheres, provided that the granules are plastic enough to allow the deformation without being destroyed. When the particles attained the desired spherical shape, the discharge valve of the chamber is opened and the granules (pellets) are discharged by the centrifugal force. The design principle of the spheronizer is relatively simple but additions and adaptations are possibility to change bowl sizes according to the requirements for the development of different batch sizes.

Drying

Pellets are dried in a fluid bed drier.

10. Continuous Flow Technology

This method does not require any liquid to start the chain reaction. In this case granulation is carried out in an inclined drum into which powder is fed at one end and granulate is removed at the other. The process produces granule with surface protected by inactive component that do not harm the sensitive API. CF technology can produce up to 12 tons of granules every day.

Advantages

1. Sensitive APIs are protected.
2. Granules and effervescent become less sensitive to humidity and high temperature.
3. Granules form extremely stable products.
4. No solvent residues in the final products.

CONCLUSION

This review article majorly focuses on the advanced granulation techniques to produce granules and pellets. Each technology has its own merits and demerits. Selection of method mainly depends on the ingredient's individual characteristics, sufficient flow properly, 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. Then the proper granulation process can be applied.

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