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Review Article on Granulation Process with Novel Technology: An overview

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ABSTRACT For making Compressed Tablet, it is necessary to prepare the material in a dry, granular form to render it suitable for passing through a compression machine. Granulation is one of the most important unit operations in the production of pharmaceutical oral dosage forms. Granulation, the process of particle enlargement by agglomeration technique, is one of the most significant unit operations in the production of pharmaceutical dosage forms, mostly tablets and capsules. Granulation process transforms fine powders into free-flowing, dust free granules that are easy to compress. Granulation process will improve flow and compression characteristics, reduce segregation, improve content uniformity, and eliminate excessive amounts of fine particles and also enhance the physical and chemical stability of the drug. High-shear wet granulation, fluidized-bed granulation, and roller compaction followed by milling are commonly used granulation techniques in the pharmaceutical industry. 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.

KEYWORDS : Pneumatic Dry Granulation, Wet granulation, Steam Granulation, Moisture-Activated Dry Granulation (MADG), Melt granulation.

Introduction

Granulation is a particle design process whereby small particles are brought together to form physically strong agglomerates. Granulation is a process in which primary powder particle are made to adhere to form larger, multi particle entity called granules. Pharmaceutical granules typically have a size range between 0.2 and 4.0 mm, depending on their subsequent use. After granulation the granules will either be packed (when used as a dosage form), or they may be mixed with other excipients prior to tablet compaction or capsule filling Depending upon the physical Characteristic of material, any one of the following method may be used for compaction of material into a tablet.

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

Great significance is still attached to wet granulation, because direct compressing is not the most suitable technology for many active substances that are in high dosages or in fine powder form. Even if the active substance is sensitive to hydrolysis, modern equipment, e.g. in a fluidized bed, eliminates all problems in wet granulation. Granulation is used mainly to improve flow and compressibility of powders, and to prevent segregation of the blend components. Particle size of the granules is mainly affected by the quantity and feeding rate of granulating liquid.

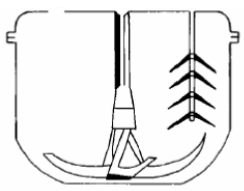
Reasons to Granulate

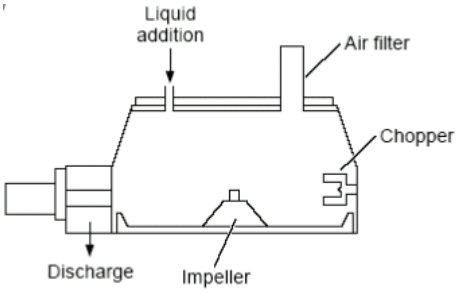
- Improve flow
- Densify materials
- Improve content uniformity
- Improve compression characteristics
- Control the rate of drug release
- Facilitate metering or volume dispensing
- Decrease dust generation and reduce employee exposure to drug product
- Improve the appearance of the tablet

Novel Granulation Technologies:

Wet Granulation: Wet granulation is the widely used technique and the granules are produced by wet massing of the excipients and API with granulation liquid with or without binder. The steps involved in conventional wet granulation technique could be seen in Fig. 4. Wet granulation has witnessed various technical and technological innovations such as steam granulation, moisture-activated dry granulation or moist granulation, thermal adhesion granulation, melt granulation, freeze granulation, foamed binder or foam granulation, and reverse wet granulation.

Steps involve in wet granulation





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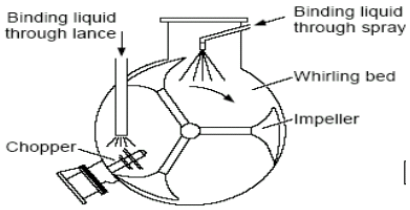


Horizontal

Recent progress in wet granulation

Steam Granulation

In steam granulation as a new wet granulation technique, water steam is used as binder instead of traditional liquid water as granulation liquid. Steam, at its pure form is transparent gas, and provides a higher diffusion rate into the powder and a more favorable thermal balance during the drying step. 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.[13,14]

Advantage:

- 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 is produced per batch.

Melt granulation

- Melt granulation or thermoplastic granulation is a technique that facilitates the agglomeration of powder particles using melt able binders, which melts or softens at relatively low temperature (50–90 °C).
- Cooling of the agglomerated powder and the consequent solidification of the molten or soften binder complete the granulation process.[31,32]
- Low melting binders can be added to the granulation process either in the form of solid particles that melt during the process.[33-35]
- Melt granulation is an appropriate alternative to other wet granulation techniques which are used for water sensitive materials[36]
- Moreover, in comparison with the conventional wet granulation process, it proposes several advantages.[31,32,34,37,38] Generally, organic or aqueous solvents are not demanded for the melt granulation process, hence the environmental requirements of organic solvent capture and recycling are eliminated, while the absence of water excludes the wetting and drying phases, making the entire process less energy- and time-consuming. Melt granulation method could be efficiently applied in order to enhance the stability of moisture sensitive drug and further to improve the poor physical properties of the drug substance.[36,39] The major drawback of this process is the need of high temperature during the process, which can cause degradation and/or oxidative instability of the ingredients, especially of the thermo labile drugs.

Moisture-Activated Dry Granulation (MADG)

This technique is a variation of conventional wet granulation technique. It uses very little water to activate a binder and initiate agglomeration.[18]

This technique involves two steps,
1) wet agglomeration of the powder particles,
2) Moisture absorption or distribution.

- Agglomeration is facilitated by adding a small amount of water, usually less than 5% (1-4% preferably), to the mixture of drug, binder and other excipients. Agglomeration takes place when the granulating fluid (water) activates the binder.
- Once the agglomeration is achieved, moisture-absorbing material such as microcrystalline cellulose, silicon dioxide, etc. is added to facilitate the absorption of excess moisture. The moisture absorbents absorb the moisture from the agglomerates, resulting in moisture redistribution within the powder mixture, leading to relatively dry granule mixture. During this moisture redistribution process, some of the agglomerates remain intact in size without change, while some larger agglomerates may break leading to more uniform particle size distribution. It does not require an expensive drying step.[19-21]
- The process does not lead to larger lumps formation since the amount of water used is very small compared to usual wet granulation. The particle size of the agglomerates is mainly accounted to be in the range of 150-500 μm. This technique is also known as "moist granulation technique" leading to confusions with the use of appropriate terminology.
- The application of MADG to an immediate-release and controlled-release dosage forms showed the advantages of wet granulation such as increased particle size, better flow and compressibility.[20,21]
- Additional advantages of this technique include wide applicability, time efficiency and less energy input, and involvement of few process variables with suitability of continuous process. However, this technique could not be used for the preparation of granules that require high drug load and for moisture sensitive drugs and hygroscopic drugs due to stability and processing problems associated with these types of drugs.

Thermal Adhesion Granulation (TAG)

- Wei-Ming Pharmaceutical Company (Taipei, Taiwan) has developed this technique, and the thermal adhesion granulation, analogous to moist granulation, utilizes addition of a small amount of granulation liquid and heat for agglomeration.[26]
- Unlike moisture activated dry granulation which uses water alone as granulation liquid, this process uses both water and solvent as granulation liquid.
- In addition to this, heat is used to facilitate the granulation process. In this process, the drug and excipient mixture is heated to a temperature range of 30–130 °C in a closed system under tumble rotation to facilitate the agglomeration of the powder particles.
- 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.[26,27] 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. Besides, this technique provides granules with better particle size, good flow properties and high tensile strength that could be directly compressed into tablets with adequate hardness and low friability. The limitations of this technique are requirement of considerably high energy inputs and special equipment for heat generation and regulation. This technique is not suitable for all binders and is sensitive to thermo labile drugs.[26-29]

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 LabsOy (Helsinki, Finland), which is described below.[6]

Pneumatic Dry Granulation (PDG)

- Pneumatic dry granulation (PDG), an innovative dry granulation technology, utilizes roller compaction together with a proprietary air classification method to produce granules with extraordinary combination of flow ability and compressibility.[6,7]
- In this method, granules are produced 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. The fine particles and/or smaller granules are separated from the intended size granules in a fractioning chamber by entraining in a gas stream (pneumatic system), whereas the intended size granules pass through the fractioning chamber to be compressed into tablets.
- The entrained fine particles and/or small granules 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 placed in a container for reprocessing later to achieve the granules of desired size.[7,8].
- PDG technology could successfully be used to produce good flowing granules for any formulations that produce compacts with a tensile strength of ~ 0.5 MPa. Also, this technology enables the use of high drug loads of up to 70-100%, because sufficient flow ability could be achieved even at lower roll compaction forces (lower solid fractions) compared to usual roller compaction.[9]

Advantage of PDG Technology

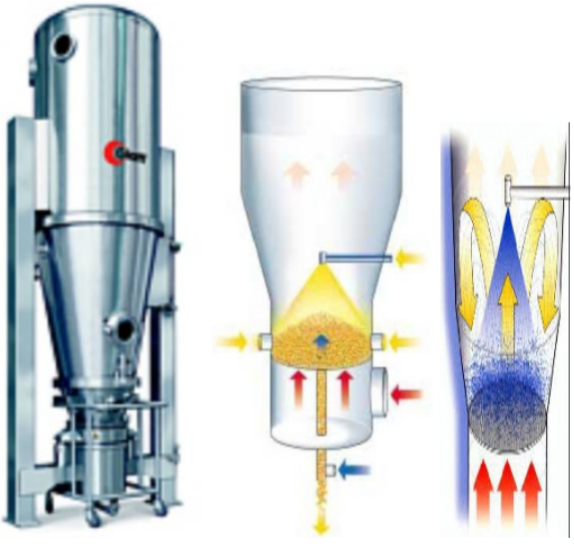
The PDG Technology has a number of advantage to support the above claims including following.

- Good granulation results even at high drug loading have been achieved with materials known to be historically difficult to handle.
- Faster speed of manufacturing compare with wet granulation.

- Lower cost of manufacturing compare with wet granulation.
- The system is closed offering safety advantage due to low dust levels and potential for sterile production or handling of toxic material.
- The end products are very stable- shelf life may be enhanced.
- The granules and tablet produced show fast disintegration properties, offering the potential for fast release dosage forms.

Granulation Techniques

- High-Shear Wet Granulation
- Fluid-Bed Granulation
- Low-Shear Wet Granulation
- Dry Granulation (Roller Compaction →Milling)
- Spray Drying
- Melt Granulation/Spray Congealing



Granulation Process Parameters

- Impeller Speed

Higher Impeller speeds generally results in denser and smaller granules. Low Impeller speeds generally result in more porous, large granules.

- Chopper Speed

Generally, Chopper speed has no significant effect on granule size and density but in cases where the chopper is large; it may function as a secondary impeller.

- Water Addition Rate and Method

Water Addition Rate is critical to granule quality. Generally, water addition rate is chosen such that local over wetting of the powder mass is not a concern and at the same time the addition rate is fast enough to accommodate processing times (~2 –5 mins for water addition).

- Massing Time

Massing time is normally in the order of 1 to 10 minutes. Long massing times (> 20 mins) may lead to decreased dissolution rates due to decreased disintegrates function or due to the formation of denser granules.

- Load of the Mixer

Generally, the load of the mixer is less than two-thirds the volume of the mixer.

CONCLUSION

The author's opinion is that the new techniques and technologies discussed in this review would need enhancements in terms of equipment, process, etc. before being industrialized successfully. Nevertheless, these could provide a platform for further technological innovation. These review works mainly focus on the novel granulation techniques to produce granule. Each technique has its own advantage and disadvantages. Which method is chosen 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. Then the proper granulation process can be applied.

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