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Review Article

NOVEL TECHNIQUES OF GRANULATION: A REVIEW

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ABSTRACT

Granulation is an important unit process in the production of pharmaceutical dosage forms like tablets, capsules and other dosage forms. Granulation process increases flow, compressibility and content uniformity of the powders. It inhibits the separation of blend components and reduces excessive amount of fine particles. This process helps to achieve improved yields with less tablet manufacturing defects. Particle size of granules depends on the quantity and feeding rate of the granulating liquid. Selecting a method of granulation requires comprehensive study of each ingredient in the formula, the combination of ingredients and their compatibility with each other is checked after, which appropriate granulation process can be applied. The recent technologies used for granulation include steam granulation, moisture activated dry granulation (MADG), moist granulation technique (MGT), extrusion-spheronization granulation, fluidized bed granulation, thermal adhesion granulation process (TAGP) and foam granulation etc. have their own advantages and overcome the disadvantages of conventional granulation process such as dust generation or deteriorating effect of heat as drying step. The objective of present work is to focus on the novel granulation technologies.

Key words: Granulation, Granulation technology, Advances, Pharmaceutical industry.

INTRODUCTION

Granulation is process making separate powder particles in to a group by using granulating fluid.[1] Granulating fluid may be water including or water heating, this depend on the nature of drug and other excipients used. The process of making of granules is granulation and technique and equipment used is granulation technology.[2-5]

Stages of granulation:[6-10]

a) **Pendular stage:** This is initial stage just after addition of binding agent.
b) **Funicular stage:**This is second stage where adequate binding solution incorporated between the particles.
c) **Capillary stage:**In this stage binding solution entrapped by capillary action. This is a perfect stage where good granules can be obtained.
d) **Droplet stage:**Here over wetting, particles may form. This stage is not desirable stage.**(**Shown in Figure 1)[4].

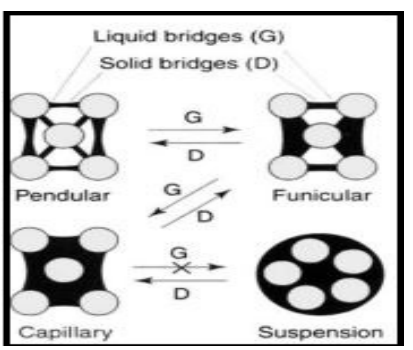


Figure 1: Stages in granulation

Classification of Granulation Technologies[11]

Basing upon the type of processing, that had been involved, GT can be classified as follows:

1. Conventional methods
   - Dry granulation
   - Wet granulation
   a) High-shear wet granulation
   b) Low-shear wet granulation
2. Novel/advanced methods
   - Moisture activated dry granulation
   - Thermal adhesion granulation
   - Pneumatic dry granulation
   - Melt/thermoplastic granulation
   - Fluidized bed granulation
   - Extrusion-spheronization granulation
   - Spray drying granulation
   - Freeze granulation
   - Foam binder granulation
   - Steam granulation

Dry Granulation

This method is cheapest method of granulation and suitable for hydro-sensitive products. In this method granules are prepared without binding solution and heat. This method involves two steps. One is preparing large particles called slugging. Second one is milling and screening of slugs into small granules. [12-16]

Advantages

a) Less equipments are needed
b) Eliminate binding solution process

Disadvantages

a) Requires specialized heavy duty tablet press.
b) Does not permit uniform colour distribution.

c) Tends to create more dust with respect to wet granulation.
d) Increases the potentiality of cross contamination.

Applications
Suitable for hydrophobic andoily substances.

Wet granulation
This method involves several steps. Initially by the addition of binding agent (hydrophilic or hydrophobic) to get wet mass. This wet mass is passed through the sieves followed by drying.[5,8]

Advantages
Easy process and no need of experts

Disadvantages
Time consuming, Labor cost is more, several steps are involved

Moisture Activated Dry Granulation (MADG)

MADG is also known as '**Single-Pot**' granulation or **moist** granulation. Here drying step is eliminated because very less amount of binding agent is used to activate binding process and moreover moisture absorbing agents like microcrystalline cellulose (MCC), potato starch, a mixture of MCC and potato starch (50% w/w), silicon dioxide, Spress® B818 Pregelatinized Corn Starch NF 17, Maltrin®maltodextrins 18, etc. used to remove moisture present in the granules.[16-18] This technology involves wet agglomeration of the powder mixture to form a tacky mass followed by moisture absorption to dry the granules. In this technology small amount of water (1–4%) is added to agglomerate the powder blend.[19,20]

Advantages
- A simple, clean, lean process that utilizes very little granulating fluid.
- Produce granules with more uniform particle size distribution (particle size range of 150-500 μm) and excellent flowability.
- Economical and time efficient, as requires less energy and eliminates drying step.
- Suitable for continuous processing, and for preparation of floating and sustained release products.

Disadvantages
- Unsuitable for thermo-labile, moisture sensitive, high moisture absorbing substances.
- Difficult to develop formulations with high drug loading.

Applications
- Suitable for eutectic and hydro-phobic substances.

Thermal Adhesion Granulation (TAG)
It is a novel GT, patented by Wei-Ming Pharmaceutical Company (Taipei, Taiwan) that involves granulation by adding very less amount of granulation fluid. In this process the binder&/diluent mixture is first wetted by pouring water or ethanol (2.0–3.6%).[17-19] Then this blend is placed in a pre-warmed glass bottle, sealed and then heated by an IR lamp to raise surface temperature of the equipment to 90^0C–105^0C for water as solvent, 70^0C–90^0C for ethanol as a binding agent and mixed under tumble rotation for 3–20 min until granules are formed. Resulted granules were immediately sifted with proper sieve 22.[21-23]

Advantages
- Requires less amount of granulation fluid and forms granules with good flow property
- Reduces the dust generation during powder processing.

Disadvantages
- Not suitable for substances with more than 130^0C melting point andfor materials with binding solvents other than water and ethanol.

Applications: Applicable in R&D systems

Pneumatic Dry Granulation (PDG):
It is a novel dry granulation method developed by Atacama Labs (Helsinki, Finland). It involves production of compact mass by using roller compaction method with little compression force. This material is introduced into a newly innovated fractionating device that separates the granules and recycles rejected fraction.[24-28]

Advantages
- Can achieve high drug loading of traditionally proven difficult materials.
- Faster development (within weeks) even with historically proven difficult materials.
- Decreases cost of product by minimizing waste through recycling and production cost.
- Excellent stability with enhanced shelf-life.
- Compatible with other technologies like coating, sustained release, fast release.
- Suitable for thermo-labile and moisture sensitive drugs.
- Taste masking and tailoring of release rate and time can be achieved.
- Produce soft and porous granules with high compressibility and Flowability.
- Possesses potentiality to handle sterile products or toxic materials
- Lowers scale-up cost and problems.

Disadvantages
- Due to usage of double compression force materials used may undergo degradation.
- High cost due to novelty in process.

Applications
- Applied widely because of compliment with regulatory bodies.
- Suitable for drugs with high melting point.

High Shear Mixture Granulation

Figure 2: Rapid mixture granulator

Rapid mixture granulator(RMG) is a simple and easily cleanable equipment developed in accordance to Good Manufacturing

Practice requirements, to reduce the cross-contamination and the environmental hazards and to get spherical and well-compacted granules in a relatively short time. This equipment can be operated in a closed unit and it involves mixing, primary and secondary granulation, drying steps. Primary granulation step involves spraying of the binding agent onto the powder bed while the secondary granulation involves kneading of the wet product to produce and to enlarge the granules. Subsequent drying of final material is done suitably under low pressure at moderate temperature. [29,30,31,32]

Impeller speed, chopper speed, water addition method and rate, massing (mixing) time, load of the RMG, feed material characteristics, drug substance particle size are the granulation process parameters that requires monitoring to get granules with desired characteristics. Volume of load in RMG should be less than two-thirds of its capacity (shown in figure 2)[4].

Advantages

- It involves Short processing time.
- Requires less amount of liquid binders required with respect to fluidized bed granulation technology.
- Highly cohesive material can be handled.

Disadvantages

- Mechanical degradation could take place in case of fragile particles.
- Results in the uneven distribution of binder solution throughout moving powder bed during high-shear granulation.
- Unsuitable for thermo-labile material.
- Over wetting leads to formation of lumps and large size granules.

Applications

- Used in pharmaceutical industry and as well as in paint, cosmetic industries

Fluidized Bed Granulation

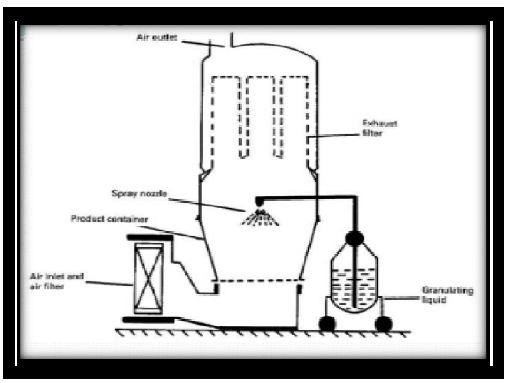


Figure 3: Fluidized bed granulator

It is an air suspension technique, of pharmaceuticals was first reported by Wurster to coat tablets that are later used for granulating and drying of pharmaceuticals and particle/granule coating. [31-34]

Fluidized bed granulation process involves spraying of binder solution onto the fluidized powder bed (FPB) to get finer, free flowing and homogeneous granules employing single equipment known as FBP. FBP contains air-handling unit, product container and air distributor, spray nozzle, disengagement area and process filters, exhaust blower or fan, control system, solution delivery system (shown in figure 3)[4].

Advantages

- Reduces dust formation during processing.
- Improves housekeeping and worker safety.
- Suitable for subsequent coating and controlled release products and reduces product loss

Disadvantages

- Cleaning was labor-intensive, time consuming and assuring reproducibility was troublesome.

Applications: Applicable for granulation, drying, coating, mixing, etc.

Extrusion-Spheronization Granulation

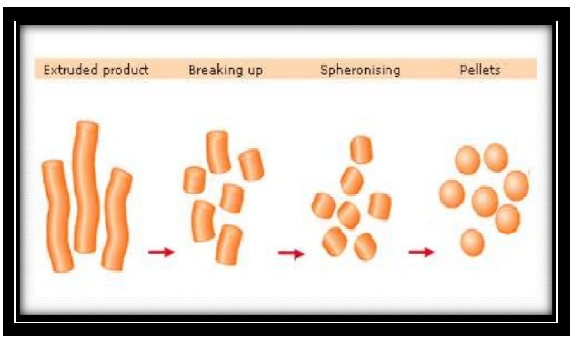
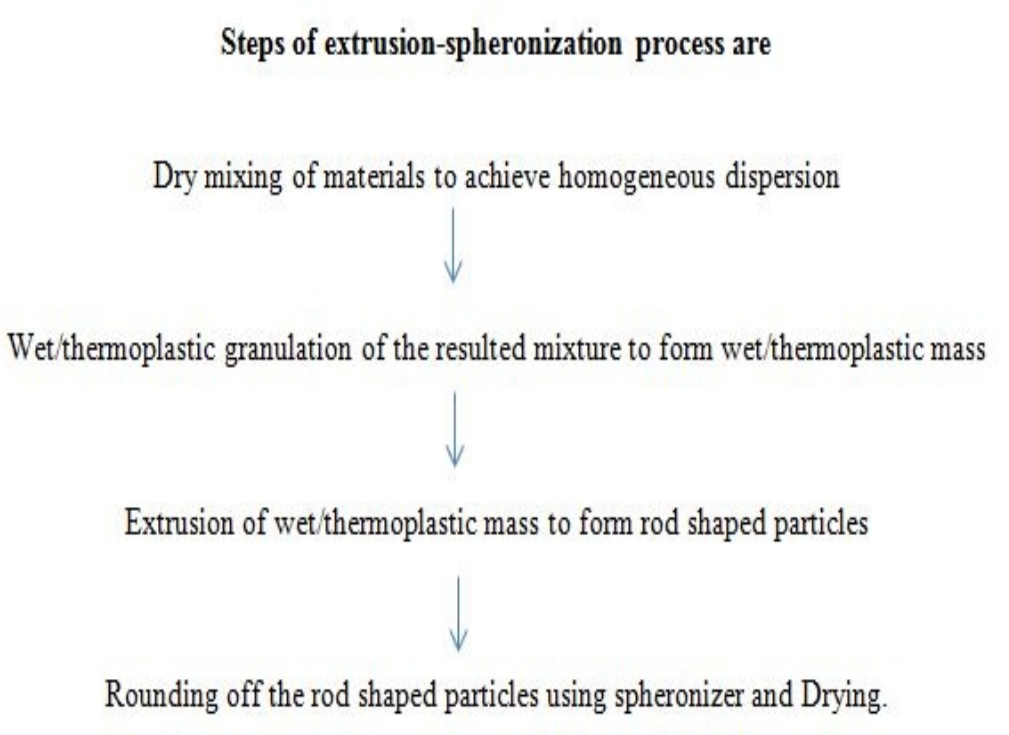


Figure 4: Extrusion-Spheronization Granulation process

A multiple step process involves five-steps capable of making uniform sized spherical particles with narrow size distribution that were suitable for controlled release formulations by extruding the tacky mass through extruder and subsequent pelletization or spheronization using pelletizer or spheronizer. [31-34] Pellets are prepared by employing wet or hot melt extrusion techniques.

Wet extrusion technique involves extrusion of wet agglomerate (tacky mass) of the powder mixture through extruder. Hot melt extrusion technique involves extrusion of thermoplastic materials through a thermostatically controlled extruder. Processing parameters like extruder pore size, spheronization speed and operational conditions need to be optimized which influences particle size, size distribution and morphology of granules (shown in figure 4)[35]



Advantages
- Incorporates higher levels of active without producing excessively larger particles
- Easy to combine two or more active agents within the same unit, in any ratio
- Modification of physical characteristics of the active ingredients and excipients
- Can produce spherical particles with high bulk density, low hygroscopicity, narrow particle size distribution and smoother surface.

Disadvantages
- Needs more labor and time for granulation
- Cannot be used for moisture sensitive and thermo-labile materials.

Applications: Used inpreparation of granules for tablets, capsules, suspensions and for dry powders.

Spray Drying Granulation

It is a continuous process where a dry granular product is obtained by feeding a binding solution or a suspension of active agent with or without excipients to the drying system where the feed is atomized and dried with a heated gas stream followed by subsequent separation of granular product from the gas stream. Alternately particle agglomeration was brought about by spraying the binder solution onto bed of powder particles in fluidized state achieved with the passage of air followed by drying using hot air. [19,20,27,28]

Advantages
- It is a fast and continuous process.
- Low cost.
- Reduces operator exposure to dust.

Disadvantages
- Substances which are sensitive to heat are poor candidates.
- Improper spray leads to inadequate sized particles.

Applications: Applicable in the preparation of dry syrups and dusting powders.

Freeze Granulation

Integrated Biosystems, Inc. (California, USA) had patented freeze GT that results in spherical and free flowing granules with optimal homogeneity. FG involves spraying of suspension containing powder into liquid nitrogen where the drops were instantaneously frozen to form granules which upon subsequent freeze-drying yields dry granules. [12-17]

Advantages
- Granule density can be controlled by the solid contents of the suspension.
- Non-oxides and metals can be handled as mild drying prevents serious oxidation.
- Results solid granules with no cavities.
- High yield with low material waste.
- Low to high quantities of granules can be produced with reproducibility.
- Equipment can be easily cleaned up and Organic solvents can be recycled.

Disadvantages

There may be a chance of degradation of drug due to use of temperature which is less than 0 ^{0}C.

Applications: In the formation of injectable granules.

Foam Binder Granulation

FBG is a simple and safer wet granulation processing of materials and employs high shear or low shear RMG, or FBP in both laboratory-scale and production-scale settings using hydroxypropylcellulose or hypromellose as binder. This technology involves continuous addition of liquid binders in the form of aqueous foam either onto the previously blended powder bed contained in RMG with variable speeds of impeller or chopper or in FPB contained in FBD. After attaining granulation endpoint the wet granules are dried in FBP till desired moisture content was achieved.

Wet foam hasphysical characteristics and flow similar to liquid and dry foam has high air-to-liquid ratio that moves more like a solid,are used for granulation; while dry foam is recommended. Foam quality was calculated from penetration time and nucleation ratio and the data is used to determine the range of acceptable foam quality that can be used to get granulated product with desired quality.[11-13,15,19,20,28,33]

Advantages

- Eliminates use of spray nozzle thereby eliminates plugging effects.
- Requires low amount of the water and the binder for granulation.
- Improves process robustness.
- Binder distribution is uniform.
- No over wetting.
- Cost effective as reduces drying, manufacturing, and equipment clean-up time, and does not require new equipment or drastic changes in processing techniques.
- Immediate release and matrix controlled-release products can be easily scaled-up.

Disadvantages: This process is success full in scale-up but it is difficult for production scale.

Applications

- Suitable for products with very low concentration or drug level (in mg or µg per tablet) as generated foam can carry active ingredients at a very low concentration,
- Suitable for water sensitive formulations, highly water-soluble and even very poorly water soluble drugs.
- Can handle historically proven difficult materials including natural ingredients used in nutritional supplements.

Steam Granulation

This technology is a simple modification of conventional wet granulation method in which steam was used as binder instead of water and involves injection of a jet of steam into the bed of fluidized particles to be granulated.[28,33,34]

Advantages

- More spherical granules with large surface area are formed thereby increases dissolution rate of the drug from granules.
- Rapid drying.
- Time efficient process.
- This Possess is complement to regulatory bodies.
- Minimizes total microorganism count.

Disadvantages

- Special equipments are required for steam generation and its transportation
- Requires high energy inputs.
- Unsuitable for thermo-labile material.
- More safety measures are required.
- Unsuitable for binders that cannot be activated by contact with stem.
- Use of temperature leads to degradation and physical changes.

Applications: Applied in the formulation of sterile products.

Advanced Granulation Equipment

Semiautomatic or fully automatic instrumentation systems had been developed and are used for optimizing each unit operation like granulation, slugging, compaction, and compression. Combining all or most of the unit operation in one system are also advanced approaches in granulation equipment technology that operates with greatest reliability. [12,13,16,21,34]

CONCLUSION

The advances in granulation technology lead to the formulation of better dosage forms in terms of content uniformity and stability aspects. Still lot of research work and study has to be done for the promotion of content uniformity, stability not only in tablets and capsules but also in dry syrups and various other formulations in Pharmaceutical industries.

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