GRANULATION PROCESS WITH NOVEL TECHNOLOGY:AN OVERVIEW

Rahul s. kapadnis* Vaibhav A. Borase**,Dr. Rishikesh S. Bachhav1*

*Department of Pharmaceutical Quality Assurance. R.G.Sapkal College of Pharmacy,Anjaneri, Nashik -422213, Maharashtra, India.

**Department of Pharmaceutical Quality Assurance. R.G.Sapkal College of Pharmacy,Anjaneri, Nashik -422213, Maharashtra, India.

1*Department of Pharmacology. R.G.Sapkal College of Pharmacy, Anjaneri, Nashik - 422213, Maharashtra, India.

ABSTRACT

Granulation For developing Compressed Tablet, it is important to develop the material in a dry, granular form to render it suitable for passing through a compression machine. Granulation is one of the most necessary unit operations in the manufacturing of pharmaceutical oral dosage forms. agglomeration technique, is used for the particle enlargement, this is one of the most significant unit operations in the production of pharmaceutical dosage forms, like tablets and capsules. Granulation process converts fine powders into free-flowing, dust free granules those are easy to compress. Granulation process will increase flow and compression property, reduce sedimantation, increase content uniformity, and remove excessive amounts of fine particles and also increase the physical and chemical stability of the API. fluidized-bed granulation ,High-shear wet granulation, and roller compaction and milling are most used granulation techniques in the pharmaceutical industry. This review article focuses on the current progress in the granulation process and technologies such as reverse wet granulation, pneumatic dry granulation, steam granulation, dry granulation, moisture-activated, freeze granulation, thermal adhesion granulation, , and foamed binder or foam

KEYWORDS :

Dry granulation ,Wet granulation, Moisture activated dry granulation, Thermal adhesion granulation, Pneumatic dry granulation, Melt/thermoplastic granulation, Fluidized bed granulation, Extrusion-spheronization granulation ,Spray drying granulation, Freeze granulation, Steam granulation,

INTRODUCTION

Granulation, it is an technique of particle size improve by agglomeration, is one of the most necessary process in the manufacturing of pharmaceutical dosage forms, mainly in capsules and Tablets. During the granulation technique, smaller fine or coarse particles are converted into large shape partical called granules. Generally, granulation commences after first dry mixing of the necessary powder ingredients along with the drug, so that a equally distribution of each ingredient throughout the powder mixture is obtained. granules used in the pharmaceutical industry have particle size in the range of 0.2-4.0 mm, they are first produced as an intermediary with a size range of 0.2-0.5 mm to be either assemble as a dosage form or be mixed with other excipients before tablet compaction.[1,2]

tablet compaction have process-related hazards, and to improve the appearance of the tablet[2] followed by the ideal characteristics of granules include circular shape for increase flow, narrow particle size distribution content uniformity and sufficient fines to fill void spaces between granules for better compaction and compression characteristics, and hardness to prevent breaking, adequate moiture and dust formation during process. Granulation is an ideal of particle design and the properties of the particles contain after granulation depend on partical size of the API and excipients, the type, concentration, and volume of binder and/or solvents, granulation time, type of granulator, drying rate , etc. The first methods in which the agglomerated granules are prepared include solid bridges, chemical reaction, sintering, and deposition of colloidal particles, crystallization. Besides, binding can also be accomplished through adhesive and cohesive forces by utilizing high viscous binders. The series of mechanisms by which granules are formed from the powder particles encompass wetting and nucleation, coalescence or growth, consolidation, and attrition or breakage.[3,4]

Reasons of granulation;

1. To prevent segregation of constituents of the powder mix

2. To improve flow properties of mix

3. To improve the compaction of mix

Classification of Granulation Technologies[5]

On the type of processing, that had been involved, granulation 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

· Steam granulation

Dry Granulation

This method is low cost method of granulation and suitable for water sensitive products. In this method granules are prepared without heat and biding solution. This method involves two steps. One is preparing large particles called slugging. Second one is milling and screening of slugs into small granules.

Advantages

- Less equipments are needed
- Eliminate binding solution process

Disadvantages

- Requires specialized heavy duty tablet press.
- Does not permit uniform colour distribut

Wet granulation

This method involves steps. First the addition of binding agent to get wet mass. This wet mass is passed through the sieves depend on drying.

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 called as 'Single-Pot' 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, Maltrin®maltodextrins 18, Spress® B818 Pregelatinized Corn Starch NF 17, etc. these are used to remove moisture present in the granules.[6,7] 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.[8,9]

Advantages

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

Disadvantages

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

Thermal adhesion granulation (TGA):

It is a novel granulation techinque 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%).[7,8] Then this blend is placed in a prewarmed glass bottle, sealed and then heated by an IR lamp to increase surface temperature of the equipment upto 900C–1050C for water as solvent, 700C–900C 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. [10,11]

Advantages

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

Disadvantages

- Not suitabs to substances with more than 1300C melting point and for materials with binding accept water and ethanol.

Pneumatic Dry Granulation (PDG):

It is a novel dry granulation techinque developed by Atacama Labs (Finland). It includes production of compact mass by using roller compaction method with small compression force. Then this mass introduced into a new fractionating device which separate the recycles rejected fraction and granules .[12,13]

Advantages

- it Can achieve high drug loading of traditionally proven difficult material .
- Faster development even with historically proven difficult materials.
- reduce cost of product by minimizing waste through recycling and production cost.
- Excellent stability with improved shelf-life.

Disadvantages

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

High Shear Mixture Granulation

Rapid mixture granulator(RMG) is a simple and easily washable equipment developed in accordance to GMP requirements, to minimize the cross-contamination and the environmental hazards and to get circular and well-compacted granules in a short time. This equipment used in a closed unit and it include mix, primary and secondary granulation, drying steps. Primary granulation step include spraying of the binding agent onto the powder bed while the secondary granulation incudes kneading of the wet product to produce and to enlarge the granules. follows the drying of final material is done suitably under low pressure at definite temperature. [14,15,16,17]

Advantages

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

Disadvantages

- Mechanical degradation may take place in case of fragile particles.
- Results the uneven distribution of binder throughout moving powder blend during high-shear granulation.
- Unsuitable for heat sansative material.
- Over wetting cause formation of lumps and large size granules.

Fluidized Bed Granulation

It is an air suspension method , of pharmaceuticals was first used by Wurster to coat tablets that are later used for granulating and drying of particle/granule coating. 17 FBD process includes spraying of binder solution onto the FPB to obtain finer granules , free flowing granulation and homogeneous granules employing only one equipment known as FBP. FBP includes air-handling unit, product container and air distributor, control system, disengagement area and process filters, spray nozzle, exhaust blower or fan,solution delivery system

Advantages

- decrease dust formation during processing.
- Increase housekeeping and worker safety.
- compitable for subsequent coating and controlled release products and reduces product loss

Disadvantages

- Cleaning needs more man power, time consuming and assuring reproducibility.

Extrusion-Spheronization Granulation

A multiple step process involves five-steps capable of making same sized circular particles with narrow size distribution that were compatable for controlled release formulations by extruding the tacky mass through extruder and subsequent pelletization using pelletizer . 17,18 Pellets are made by employing wet or hot melt extrusion techniques.Wet extrusion technique includes extrusion of wet agglomerate of the powder mixture in to the extruder. Hot melt extrusion technique includes extrusion of thermoplastic materials in to the a thermostatically controlled extruder. Processing parameters like extruder pore size, spheronization speed ,operational conditions need to be optimized which influences size distribution ,particle size, and morphology of granules 18

Advantages

- Includes higher levels of active without producing excessively larger particles
- Easy to mix two or more active agents within the same unit, in any ratio
- Modification of physical characteristics of the API and excipients

Disadvantages

- Needs more man power and time for granulation
- Cannot be used for hygroscopic and thermo-labile materials.

Spray Drying Granulation:

It is a continuous process in which a dry granular product is obtained by feeding a binding solution or a suspension of API with or without excipients to the drying system where the feeding is atomized and dried with a hot gas stream then subsequent separation of granular product from the gas stream. Alternately particle agglomeration is bring about by spraying the solution of binder onto power bed particles in fluidized state achieved with the passage of air followed by drying using hot air. [12,17]

Advantages

- It is continuous process and fast.
- cost effective
- Reduces operator exposure to dust.

Disadvantages

- material which are heat sensitive are poor candidates.
- Improper spray caused inadequate sized particles.

Freeze Granulation

Integrated Biosystems, had patented freeze granulation techinque that results in circular and free flowing granules with great homogeneity. freeze granulation includes spraying of suspension consist powder into liquid nitrogen where the drops were quickly frozen to form granules which upon freeze-drying yields dry granules. 12,17

Advantages

- Granule density controlled by the solid contents of the suspension.
- metales and Non-oxides can be handled as mild drying prevents serious oxidation.
- Results solid granules with no cavities.

Disadvantages

There may be a chance of degradation of drug due to use of temperature which is less than 0 degree

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

Advantages

- More circular granules with large surface area are formed and increases dissolution rate of the drug from granules.
- fast drying.
- required less time.
- complement to regulatory bodies.
- decrease total microorganism count

Disadvantages

- Special equipments are needed for steam generation and its transportation
- need high energy inputs.
- Unsuitable for heat sensative material.
- More safety measures are needed.

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