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A Review: High shear granulators for Tablet Dosage Form Development

Bhanu N*

Department of pharmaceutics, Bapatla college of pharmacy, Andhra Pradesh, India.

Research Article

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*For Correspondence

Bhanu N, Department of pharmaceutics, Bapatla college of pharmacy, Andhra Pradesh, India. Tel: 919052381235;

E-mail: bhanunagendla@rediff.com

E-mail: rrajesh245@gmail.com

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ABSTRACT

Granulation, is a significant unit operations in the production of pharmaceutical finished products, mostly tablets and capsules. Generally, granulation process can be done either through Wet granulation or by Dry granulation. Many of the product formulators considers wet granulation as a universally applicable method for tablet production. The final blend of a compression mix generally requires a good flow, good compactability, uniform distribution of drug and controllable drug release which can be obtained with wet granulation without relying on the intrinsic properties of the drug or the excipients. In high shear granulators, all the process of dry -mixing and granulation can be done in a few minutes and the if required the systems can be connected with a variety of devices to detect the end point of granulation. This article deals with the basics of the wet granulation technique mostly by using high shear granulators

INTRODUCTION

In granulation process, fine particles or coarse particles are converted into large agglomerates called granules. Hence, the granulation can be defined as ‘‘a process whereby small powder particles are gathered to form larger, multiparticulate entities. Granulation, is a significant unit operations in the production of pharmaceutical finished products, mostly tablets [1-10] and capsules. The objective of granulation process is to combine ingredients to give a quality product. The principle behind granulation is size enlargement process that converts small particles into physically stronger & larger agglomerates.

Reasons for granulation

1. increase the content uniformity of drug distribution in the product

2. increases density of the material

3. enhance the flow property and compression characteristics.

4. reduces dust and environmental contamination

5. improves the product appearance

6. Lower compression pressure, less wear and tear on tooling

7. Lower pressure weight, less wear and tear on tooling

Choice of methods for granulation

Granulation is a key processing step in the production of many solid dosage forms [11-13]. Generally, granulation process can be done either through Wet granulation or by Dry granulation. These two granulation techniques have their own advantages and disadvantages.

Wet granulation

Wet granulation process involves the mixing of dry powder blend with granulating fluid. The fluid used for granulation process [14-30] must be volatile so that it can be removed after drying and it should be nontoxic in nature. Liquids used for granulation process include water, isopropanol, and ethanol. These liquids can be added alone or in combination. The granulation liquid may be used alone or, it may contain a dissolved adhesive (binders) which is used to ensure particle adhesion once the granule is dry. Binder plays an important role in tablet formulation as they help in linking particles to one another. It is utilized for converting powder into granules. Additions of binders can be either as a dry powder form or it can be added to granulating fluid i.e. either as solids or as liquid solution

Dry granulation

In dry granulation, [31-38] the particle size is enhanced by subjecting the powder particles under high pressure. The two types of dry granulation are 1) large tablet (known as slug) is produced in a heavy-duty tableting press (slugging) or the powder is forced between two counter rotating rolls to deliver a ribbon like materials (roller compactor, usually referred to as an chilsonator). In both the cases the slugs or compacts are size reduced using a suitable milling technique to produce granules, which is usually sieved to yield the required size fraction. The fines material obtained can be reworked to avoid wastage. Dry granulation is an attractive process for API's that are moisture sensitive or temperature sensitive and it can be applied in continuous granulation processes. There has been not much progress in the dry granulation technique in comparison to wet granulation, except for one important innovation known as pneumatic dry granulation technology, an innovative dry granulation technology, which produce granules with good flowability and compressibility. When the materials/ blend is dry granulated, processing time is reduced. equipment requirements are streamlined, there-fore, the cost of the final product gets reduced. The major disadvantage with dry granulation is higher percentage of fines or non-compacted products, that may lead to compromised tablet quality.

Purpose of wet granulation

Many of the product formulators considers wet granulation as a universally applicable method for tablet production. The final blend of a compression mix generally requires a good flow, good compactability, uniform distribution of drug [39-48] and controllable drug release which can be obtained with wet granulation without relying on the intrinsic properties of the drug or the excipients. For high dose drugs, which has poor flow and poor compressibility of the active mean can be manufactured by wet granulation and for low dose (high dilution) drugs the current preferred drug product processing method is wet granulation process in which the drug particles get locked into the granules and thus reduces the segregation intensity and poor content uniformity.

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Lesser amount of liquid binders required compared to Fluid bed granulator

There are therefore a number of advantages with wet granulation, but there also a number of disadvantages. Granulation Fluid used in the processes can bring many unnecessary changes in drugs or in excipients; It is an expensive process due to time consuming, equipment, energy, labour and space requirement. Material loss during different stages of processing. In case of moisture sensitive drugs stability can become a major concern. Increase in temperature can lead to chemical degradation of thermolabile materials. Over wetting can cause formation of granules with large size. As the processing steps are many in wet granulation, it increases the number of quality critical factors that need to studied and controlled in a QbD development programme.

Types of Wet granulation

Wet Granulation can be a low or a high shear process, including fluid bed granulation. Traditionally, Wet Granulation is a batch process that is controlled based on process parameters. Each process has its own strengths and weakness which may be useful for different formulations [49-58], but in practice a formulator may not have the decision of which process to use for a product, the selection being determined by equipment availability and company's choice based on their experience.

Low Shear Granulation

This granulation technique employs low speed planetary or trough mixers in which the active pharmaceutical ingredient and intra granular excipients are granulated with a binder solution [59-70], the resulting wet mass is screened to form discrete granules and are dried in tray drier. The dried granules are rescreened or milled to the desired size, mixed with extra granular excipients then blended, lubricated, and compressed. The main disadvantages of this process are the openness of the equipment and the manual transfer of the materials, the long drying times, potential for migration of soluble components in tray drying (2) and the general lack of instrumentation for in-process control.

High shear granulation

A high shear granulator consists of a cylindrical mixing bowl, a three bladded impeller, a chopper, an auxillary chopper, a motor to drive the blades and a discharge pot. The steps involved in high shear granulator

1)Dry mixing of the powder blend

2)Addition of binder solution or granulating fluid

3)Wetting of the powder and nucleation process

4)Granules growth and Powder densification

5)Breaking down the large lumps formed

The impeller which is used for mixing powder blend generally rotates at a speed ranging from 100 – 500 rpm and exerts high shear and compaction forces on the blend. The high-speed chopper rotates at 1000 – 3000 rpm which breaks the wet mass as the granulation process continues. Thus the combination of impeller and chopper blades (figure 10) gives effective mixing of components and minimizes the amount of water to be added compared to low shear granulation [70-76].

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Figure 1: High shear granulator mixing bowl with impeller and chopper blades.

The major advantages of these high shear mixers are the decreased time process and the production of very dense granules with low All the process of dry -mixing and granulation can be done in a few minutes and the if required the systems can be connected with a variety of devices to detect the end point of granulation.

The advantages of high shear granulators are 1) Applicable to almost all kind of formulations.2) Granulation process requires less binder. 3)Within short span granulation can be achieved. 4) The effect of over granulation can be reduced to some extent by milling the dried granules. 5) A better granulation can be a light granulation but with good flow.

The disadvantages of high shear granulators. 1) Over wetting of granules can lead to formation of large lumps. 2) Degradation of thermolabile materials may be possible due to increase in temperature. 3) As the water gets intimately mixed with the formulation components, changes in the drug and excipients can occur. 4) It has narrow range of operating conditions.

End point Determination

The important control in granulation process is to achieve the required granulation consistency by determining the granulation end point which is achieved by monitoring the power consumption of the impeller motor, even many other methods have been investigated. Endpoint can be defined as a target particle size mean or distribution.

Traditional Methods for detecting the end point

a) ***Power Consumption*** - Power consumption of the mixer motor for end-point determination and scale-up is widely used because the measurement is economical, does not require extensive mixer modifications and is well correlated with granule growth

b) ***Impeller Torque*** - Requires installation of strain gauges on the impeller shaft or on the coupling between the motor and impeller shaft. Since the shaft is rotating, a device called a slip ring is used to transmit the signal to the stationary data acquisition system.

c) ***Torque Rheometer*** - A torque rheometer provides an off-line measurement of torque required to rotate the blades of the device and can be used to assess rheological properties of the granulation. The torque values obtained have been termed a “measure of wet mass consistency”.

d) ***Reaction Torque*** - As the impeller shaft rotates, the motor tries to rotate in the opposite direction, but does not because it is bolted in place. The tensions in the stationary motor base can be measured by a reaction torque transducer.

Optimisation in Wet Granulation

Many variables in wet granulation method affects the physical properties of the granules and tablets.

Apparatus variables

Apparatus variables such as the size and shape of the bowl, impeller and chopper are dependent on the type of mixer used. The effects of the impeller model in high-speed mixers can be described in terms of volume swept out by the impeller. A high swept volume causes increased densification of the agglomerate and narrow granule size distribution. The size of the Chopper and rotation speed had no effect upon the granule size distribution.

Process variables

Granulation in a high shear granulator is mainly controlled by the mechanical forces on the moist powder mass by the mixing tools. The major variables effecting the granules properties are the impeller speed and wet massing time. The combined effect of these two variables can be understood in terms of liquid saturation.

Impeller Speed - High Impeller speed generally results in more dense and small granules. Low impeller speed generally results in more porous and large granules.

Chopper Speed - Chopper speed has no significant effect on granule size and density but if the chopper is large, it may act as a secondary impeller.

Water Addition Rate and Method - Water Addition Rate is critical to granule quality. The water addition rate is chosen that the over wetting of powder mass is not a concern and the same time it is fast enough to accommodate processing times.

Massing Time – kneading of the wet mass can be done normally for 1 to 10 minutes. Long massing times may lead to decreased dissolution rates which is due to decreased disintegrant functionality or formation of dense granules.

Fluidised Bed Granulation

Granulation is a size enlargement procedure that a fine powder integrates into larger granules with a specific size and shape. Fluid bed granulation is a process by which granules are produced in single equipment by spraying a binder solution onto a fluidized powder bed. In this process drug and excipients are loaded into a fluid bed processor, fluidised with air, and the granulating fluid is sprayed into the bed, usually from above, with a continuous stream of warm drying air. This is a three-stage process of 1) Blending, in which the drug and excipients are dry mixed with low volume of fluidising air to achieve blend homogeneity and to warm the dry powders. 2) Granulation, in which binder solution is sprayed onto the fluidised bed [77-81]. Growth of granule during this phase depends on a number of factors such as granulating fluid viscosity and droplet size and spray rate. 3) Drying, in which the spraying is stopped and the powder bed is gently fluidised until the granules dries. With the bed temperature, we can determine the end point.

Advantages of fluidised bed granulation

It is a contained process, that a single piece of equipment may be used for granulation and drying, thus representing a cost effective over high shear granulation. Fluid bed granulation improves the manufacturing process, because it produces uniform particles with specified particle size, loss of drying (LOD), and other required variables. The process is cost effective

since the equipment combines both granulation and drying, and thus reducing the space required for a product. It reduces material loss. It reduces dust formation during the entire processing.

Disadvantages of fluidized bed granulation

Fluid Bed cleaning is labor-intensive and time consuming. Difficulty of assuring reproducibility. In certain cases, premix has to be prepared as certain materials are incapable of being mixed by fluidization before granulation.

CONCLUSION

In many pharmaceutical industries, the high shear granulators are used for blending and Granulation. The use of wet granulation technique, has been going on traditionally since many years it has been universally applicable method for tablet production.

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