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Short communication

Critical process parameters in wet granulation

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Introduction

Granulation is the process of agglomeration of a powder mixture, which results in the enlargement of the particles. Wet granulation is considered one of the most important processes in the production of solid dosage forms. The wet granulation process offers several advantages such as enhanced flowability, improved compatibility, reduced segregation, and less dust. The most commonly used wet granulation techniques are high shear and fluid bed granulation. A commonly employed high-shear granulation process requires multiple unit operations, such as drying and sieving after wet granulation. The preferred drying method is fluid-bed drying.

The wet granulation process that occurs in high-shear granulators can be divided into three main stages: wetting and nucleation, consolidation and coalescence, attrition, and breakage. When the liquid binder is added to the powder mass, particles start aggregating and form some clusters (nucleation). The liquid binder acts as a bridge between clusters and forms granules. The granules further undergo compaction to form solid particles (consolidation). Aggregation is the primary term in granulation, which results in the formation of larger particles (agglomerates) by aggregating smaller particles. When exposed to the shear field, larger agglomerates break into smaller granules. Other continuous particle size change mechanisms are layering, causing size increase, and attrition, causing size decrease. However, their rate and processing times vary significantly depending on the field properties termed critical process parameters (CPPs) within the respective granulation system.

Effect of raw materials on wet granulation process and granule properties

The formulation variables and granulation process should be controlled to produce granules with the desired properties. Since granule formation in wet granulation is dependent on the degree of liquid saturation, the factors that influence the degree of liquid saturation should be optimized to obtain an optimal granulation formulation. The factors that affect the degree of liquid saturation are formulation, process, and apparatus variables.

In the powder mixture of a tablet formulation are included API and excipients such as a filler (or fillers), a disintegrant, and a binder. The physical properties of the granules are influenced by the physical properties of raw materials in the powder mixture, such as particle size, particle size distribution, particle shape, surface morphology, and surface area. The total surface area of the starting materials, related to the particle size and porosity of the starting materials, will affect the amount of liquid binder required for granulation. The liquid adsorption of the starting material could also affect the amount of liquid binder required for wet granulation. Therefore, the amount of binder solution required for granulation depends on the formulation composition and the physical characteristics of the starting materials.

A binder is normally required for the wet granulation process. The binder can be added to the powder mixture as a dry powder followed by the addition of water, or an appropriate solvent to activate binding. Alternatively, the binder can also be added to the powder mixture as a binder solution. The bonding characteristics of the binders used for wet granulation could vary due to the differences in their physicochemical properties. Therefore, the type of binder used for granulation can influence the granulation process, the amount of binder required for granulation, and the physical properties of the obtained granules. The amount of binder and granulating liquid used during granulation affects the granulation process and the physical characteristics of the prepared granules. Generally, an increase in binder concentration could result in the production of larger granules (Juppo et al., 1992).

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Granule friability is also influenced by the binder concentration and the amount of granulating liquid added to the formulation during granulation (Hariharanand et al., 2002). Granule friability decreased with an increase in the binder level. An inverse relationship was observed between granule friability and the amount of water added to the formulation, especially at lower drug concentrations.

Critical process parameters

Several factors affect product physicochemical characteristics and quality such as the load of the granulator bowl, impeller speed, granulating solution addition method, granulating solution addition rate, chopper speed, and wet-massing time.

Impeller speed is one of the process parameters in high shear granulation. The main function of the impeller is to agitate the powder bed and to get uniform distribution of the binding solution. Selection of optimum impeller speed might be critical to obtaining granules with desirable physical properties as insufficient impeller speed leads to uneven distribution of binder resulting in uncontrolled granule growth. Similarly, wet-massing time also has a crucial role to control the properties of granules and tablets. Longer wet-massing time could generate granules with higher density and strong granules. Hard granules might reduce the disintegration and dissolution time of tablets. Chopper size and rotation speed had no effect on the granule size distribution because the primary function of the chopper is to disturb the uniform flow pattern of the mass. The mode of addition of the liquid binder can affect the characteristics of the granules. When water, used as a binder liquid, was added to the powder mixture by atomization, granules with a slightly narrower particle size distribution were obtained. An inadequate amount of liquid binder or water gives weak, fragile granules with a high percentage of fines, whereas excess water results in over-wetting forming hard, dense, and uncontrolled granule growth. The amount of water used in granulation is mainly dependent on the drug and excipients properties and its composition in the formulation. The amount of water can be optimized by observing the change in power consumption or change in torque profile, which has been proven to be a reliable control method because it correlated with the different stages of wet-massing time (Badawy et al., 2000).

Granulation end-point determination

Several different approaches have been explored for the determination of granulation end-point. These approaches can be classified into two major categories: indirect measurements and direct measurements.

In the indirect measurements, the electrical and mechanical parameters of the granulator motor are monitored since the changes in these parameters are related to the changes in the consistency of the powder mixture in the wet granulation process. The electrical characteristics of the motor are motor current and power consumption. The mechanical characteristics of the motor are torque and tachometry. Power consumption used as granulation end point control has been related to the level of liquid saturation of the moist agglomerates, densification of wet mass, and granule growth. Leuenberger proposed that the liquid amount required for granulation corresponds to the plateau in the power consumption record profile (Leuenberger, 1982). In the direct measurements, the physicochemical properties of the powder mixture are monitored during the wet-granulation process. These properties could be mass conductivity and granule size.

Conclusion

Wet granulation is one of the most important unit operations in the production of solid dosage forms. The properties of the raw materials and critical process parameters have a significant impact on the final granule properties during the process of wet granulation. All these process parameters should be controlled during the production process. Various innovative approaches have been explored to simplify and control the granulation process and improve the quality of the produced granules. Future advancements in the equipment and granulation techniques could further improve the granulation process, thus resulting in a better quality of the granules.

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