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Review

A review of monitoring methods for pharmaceutical wet granulation

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ABSTRACT

High-shear wet granulation is commonly used in the pharmaceutical industry to improve powder properties for downstream processes such as tabletting. Granule growth, however, is difficult to predict because the process is sensitive to raw material properties and operating conditions. Development of process analytical technologies is encouraged by regulatory bodies to improve process understanding and monitor quality online. The primary technologies investigated for high-shear wet granulation monitoring include power consumption, near-infrared spectroscopy, Raman spectroscopy, capacitance measurements, microwave measurements, imaging, focused beam reflectance measurements, spatial filter velocimetry, stress and vibration measurements, as well as acoustic emissions. This review summarizes relevant research related to each of these technologies and discusses the challenges associated with each approach as a possible process analytical technology tool for high-shear wet granulation.

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1. Introduction

Wet granulation is a process for size enlargement, where small primary particles are joined together using agitation and a liquid binder. The purpose is to improve the properties of very fine cohesive powders used in products such as pharmaceuticals, ceramics, detergents and fertilizers (Litster et al., 2004). Granulation is commonly used in the pharmaceutical industry during tablet manufacturing. Fine powders are granulated to improve flow during tabletting and reduce the potential for dusting. The formation of granules also helps to reduce segregation and improve the content uniformity of the final product (Sherrington and Oliver, 2006).

There are three main types of granulators used in pharmaceutical manufacturing: tumbling granulators, fluidized-bed granulators and mixer granulators. In tumbling granulators, such as drum and disc granulators, particles are agglomerated by a tumbling motion resulting from the combination of gravity and centrifugal forces. Tumbling granulators are able to accommodate large batch-sizes but cannot be used to manufacture granules smaller than 1 mm. In fluidized-bed granulators, air is used to agitate the particles while spraying binder through a nozzle located above, inside, or below the powder bed. The agitation is less aggressive than mechanical mixing and the granules are

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typically more porous (Gao et al., 2002; Snow et al., 2008). In mixer granulators, agglomerates are formed by mixing a bed of powder with an agitator while adding a liquid binder. The intensity of the motion produces granules that are smaller, denser, and often more spherical than granules from tumbling or fluidized-bed granulators (Flore et al., 2009; Agnese et al., 2010; Morin and Briens, 2014). The added intensity reduces the amount of liquid required, leading to shorter drying times. Examples include low-speed mixers, planetary mixers and high-speed mixers.

High-speed mixer granulators, or high-shear granulators, are used extensively in the pharmaceutical industry because they are capable of producing granules that are small (typically less than 1 mm) and dense, making them ideal for blending and tabletting. In addition, a wide range of materials can be accommodated, including cohesive or sticky powders, and viscous binder solutions. High-shear granulators are usually operated in batch mode with a vertical mixing shaft. Characteristic features of a typical high-shear granulator include a stainless steel granulator bowl and a central impeller blade, used to agitate the powder and promote densification. The speed of rotation is typically between 60 and 800 rpm, depending on the equipment scale, and corresponds to tip speeds of approximately 10 m/s (Litster et al., 2004). A chopper blade may also be located off-center to help break apart large agglomerates or promote growth of smaller particles. The speed of rotation for the chopper is typically between 500 and 3500 rpm (Litster et al., 2004; Reynolds et al., 2007). This review focuses on monitoring methods that can be applied to pharmaceutical high-shear wet granulation.

In high-shear granulators, powder flow is initiated by the transfer of momentum from the impeller to the powder and propagated by a series of particle–particle and particle–equipment collisions (Sato et al., 2008). The flow of fine, unfluidized powder is poorly understood and as a result there are no generally accepted models for predicting flow patterns during granulation (Litster et al., 2004). A study by Litster et al. (2002) using a high-speed camera and imaging software, defined two flow regimes for dry powder in vertical shaft mixers, bumping and roping. Bumping occurs at low impeller speeds and is characterized by the up and down movement of the powder bed as the impeller blades pass underneath. The bed of powder rotates slowly but little vertical turnover is observed. Roping occurs at higher impeller speeds and is characterized by a toroidal motion, where material is forced up the vessel wall and then collapses back down towards the center.

Studies of flow behavior during granulation show particle velocities and the forces acting on particles vary with axial, radial and tangential location, as well as binder volume (Sato et al., 2008, 2011; Plank et al., 2003; Darelius et al., 2007). Sato et al. (2011) used positron emission tracking to show particle velocity is proportional to the speed of rotation near the impeller and significantly less proportional near the surface. They also showed there are different regions of size-dependent flow within the granulator. Plank et al. (2003) studied the velocity of particles at the surface using a high-speed camera and found the velocity increases when the particles first become cohesive and again at the transition to dense agglomerates. Darelius et al. (2007) used a high-speed camera to show friction is inversely related to cohesion. When water is added the liquid acts as a lubricant and friction between the powder and the wall is reduced. As a result, the introduction of a liquid binder is thought to add additional complexity to granule flow behavior.

Granulation takes place according to three different rate processes: wetting and nucleation, consolidation and growth, and attrition and breakage. Wetting refers to the initial introduction of liquid and the attempt to evenly distribute it throughout the blend. Nucleation occurs when the liquid joins together nearby primary particles in weak structures known as nuclei. The nuclei form the basis for granule growth, which occurs when particles and/or nuclei collide and stick together. Whether a collision results in coalescence depends on a number of factors, including the mechanical properties of the granules and the availability of liquid at the granule surface (Snow et al., 2008; Iveson et al., 2001a). Studies show granule growth increases exponentially when the pore saturation reaches between 80 and 100% (Litster et al., 2004). As granules grow, they also consolidate due to the agitation forces present with mixing. Consolidation increases the granule strength and forces excess liquid to the surface. Agitation can also cause breakage in granules that are weak or poorly formed. In addition, dried granules may undergo attrition or breakage during downstream processing or handling (Snow et al., 2008; Iveson et al., 2001a).

The rate processes in granulation take place in a series of stages. The system starts out as a mixture of dry powder and nucleation begins once the liquid binder is introduced. Nucleation is followed by granule growth, which typically proceeds according to either a steady growth or induction mechanism. Steady growth is characterized by a linear increase in granule size and has been observed in systems where the granules are weak and deformable. The elastic nature of the granules results in large contact areas during collisions, promoting coalescence. If saturation exceeds a critical level, steady growth will transition to rapid growth. Induction growth is characterized by a delay period, where there is relatively little change in granule size. The granules are not as deformable and must consolidate until a sufficient amount of liquid is present on the granule surface, at which point rapid growth occurs. From rapid growth, both steady and induction systems can become over wet masses or slurries if saturation is continued (Iveson et al., 2001a, 2001b). The transition from steady or induction growth to rapid growth and over wetting often occurs quickly and can be affected by minor changes in material inputs or process parameters. As a result, maintaining consistent product attributes is often a challenge (Litster et al., 2004; Snow et al., 2008). Factors shown to affect granule growth include the initial particle size distribution, binder content, binder surface tension and impeller speed (Iveson et al., 2001a). Development of an online system to monitor granule growth would help accommodate inherent process variability and improve control.

2. Process analytical technologies

The complexity of the high-shear granulation process makes it difficult to measure product quality during processing. As a result, current pharmaceutical development and manufacturing practices rely on a series of offline tests to determine whether a final product meets quality requirements. The Food and Drug Administration (FDA) and other regulatory organizations, however, are encouraging the development of process analytical technologies (PATs) to acquire process data online and build quality assurance into the manufacturing process. The objective is to promote increased understanding of pharmaceutical processes and sources of variability. By increasing understanding it would be possible to design more robust manufacturing practices, where instead of placing tight controls on process inputs, operating parameters could be adjusted to accommodate variability and achieve consistent product quality (U.S. Department of Health and Human Services, 2008).

Development of PATs requires an understanding of the physical and chemical properties affecting product quality, as well as how these properties are influenced by changes in process parameters, such as impeller speed or binder volume. A design space approach is recommended to understand the interaction of various input variables and process parameters in relation to product quality (U.S. Department of Health and Human Services, 2008). As shown in Fig. 1, the design space is a subset of the knowledge space, where the knowledge space represents what is known about the process,

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