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Scale-up of a high shear wet granulation process using a nucleation regime map approach

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ABSTRACT

Scale-up of the high shear wet granulation (HSWG) process is considered a challenge because HSWG is complex and influenced by numerous factors, including equipment, formulation, and process variables. For a system of microcrystalline cellulose and water, HSWG experiments at three scales (1, 2, and 4 L working vessel) were conducted with a granulator. Scale-up was implemented on the basis of a nucleation regime map approach. To keep dimensionless spray flux and drop penetration time constant, water addition time at three processing scales were 300, 442, and 700 s, respectively. The other process parameters were kept unchanged. Granule size distributions were plotted and compared, and scanning electron microscopy was used to analyze granule surface morphology. Physical characterization was undertaken using a modified SeDeM method. At nearly all scales, granule yield was greater than 85% and all the cosine values were larger than 0.89. At the same experiment points, granules at all scales had similar surface morphology and similar physical characteristics. The results demonstrate that a rational scaling-up of the HSWG process is feasible using a regime map approach.

Introduction

High shear wet granulation (HSWG) is widely used in the pharmaceutical industry for the preparation of solid medicines. HSWG is used to enlarge primary particle size and convert fine cohesive powder into dense free-flowing round granules that have certain desired characteristics, including: bulk density, dissolution, strength, and compaction properties. Scale-up of granulation processes is difficult and often problematic owing to the inherently heterogeneous nature of the materials used. To successfully scale-up HSWG, process modeling is indispensable, and there are three different quantitative engineering approaches to do this as discussed by Kayrak-Talay and Litster (2011), as shown in Table 1.

For the HSWG process, formulation design and process scale-up can be undertaken with a regime map approach based on dimensional analysis. In regime map theory, as proposed by Iveson and Litster (1998), the rate processes for HSWG consist of wetting and nucleation, coalescence and growth, and breakage. Because the growth regime map is based on operating in the drop-controlled regime for wetting and nucleation (Hapgood, Litster, & Smith, 2003), only the wetting and nucleation regime map was considered in this study.

Two critical competing processes affect nucleation. One is the competition between the rate at which new powder is exposed to the spray and the rate at which the liquid binder is sprayed onto the powder bed (Litster et al., 2001). A dimensionless parameter, Ψ_a, is introduced to quantify the relative significance of these two competitive rate processes, which is defined as

$$\Psi_a = \frac{3\dot{V}}{2\dot{A}d_d}, \quad (1)$$

$$\dot{A} = vw, \quad (2)$$

where $\dot{V}$ is the volumetric spray flux, $\dot{A}$ is the powder surface refreshing flux, d_d is the spray drop diameter, v is the particle velocity, and w is the spray width. If the value of Ψ_a is large, it means

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Table 1
Quantitative engineering approaches for process scale-up and design (Kayrak-Talay & Litster, 2011).

What do we know?	How do we design experiments and scale?	Implications
Nothing except parameters we can vary	Statistical experimental design	Many experiments at all scales
Controlling mechanisms	Careful formulation and process characterization; Designing experiments based on dimensionless groups and regime maps	Reduced experiments at all scales Use dimensionless groups to scale-up
Fully predictive model	Careful formulation and process characterization; Design minimum number of experiments to validate and fine tune the model	Least number of experiments Pilot/full scale model validation and parameter estimation

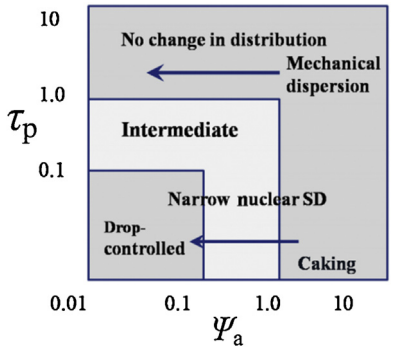

Fig. 1. Nucleation regime map. Ψ_a is the dimensionless spray flux, and τ_p is the dimensionless drop penetration time. SD: size distribution (Hapgood et al., 2003).

that the drops cover the powder bed at a rate faster than the rate at which the bed surface can be refreshed. As a result, one nucleus may be formed by two or more drops, and drop coalescence will occur on the powder bed surface.

The other competing process is illustrated by the dimensionless drop penetration time that is the ratio of the rate at which binder drops penetrate into the powder bed to the rate at which these drops are re-exposed to the spray (Hapgood, Litster, Biggs, & Howes, 2002; Hapgood et al., 2003). The dimensionless drop penetration time τ_p is defined as

$$\tau_p = \frac{t_p}{t_c}, \quad (3)$$

where t_p is the time a drop takes to fully penetrate into the powder bed and t_c is the time the exposed powder surface takes to circulate back to the spray zone. The value of τ_p is determined by both the formulation attributes and the process factors, and is a measure of the thermodynamic and kinetic interactions between the liquid binder and the powder bed for granulation. If the value of τ_p is large, a drop can coalesce with another drop before it completely penetrates into the powder bed and leaves the spray zone even though Ψ_a is small, which will result in lumps because of uneven distribution of the binder.

Nucleation behavior can be well described in the regime map (Hapgood et al., 2002, 2003). The coordinates of a two-dimensional nucleation regime map are the dimensionless spray flux Ψ_a and the dimensionless drop penetration time τ_p. As can be seen in Fig. 1, there are three regimes of nucleation on this map: the mechanical dispersion regime, the intermediate regime, and the drop controlled regime. When either Ψ_a or τ_p is large, a mechanical dispersion regime occurs, whereby caking and undesirable agglomerates take place and excess binder drops coalesce on the powder bed surface. When Ψ_a and τ_p are decreased, nucleation shifts into the intermediate regime. In this regime, drop coalescence and granule size distribution are improved. When both Ψ_a and τ_p are small, a drop controlled regime occurs. In this regime, only one nucleus is formed by a single liquid drop, which results in well-controlled nucleus formation and a narrower granule size distribution.

Table 2
Geometrical parameters of three vessels for the granulator.

Scale (L)	Inner diameter (mm)	Depth (mm)	Impeller radius (mm)	Chopper group
1	140	165	70	2
2	190	165	95	3
4	240	165	120	4

Some studies have validated the nucleation regime map in the formulation design of blank granules and drug-loaded granules (Ax, Feise, Sochon, Hounslow, & Salman, 2008; Hapgood, Farber, & Michaels, 2009; Hapgood, Amelia, Zaman, Merrett, & Leslie, 2010). However, few examples have been reported to solve the scale-up problems of HSWG process using a regime map approach (Kayrak-Talay, Dale, Wassgren, & Litster, 2013; Litster et al., 2002). In this study, we examined the application of the regime map approach to the scale-up of the HSWG process, and the validation of the nucleation regime map across different granulation scales.

Experimental

Materials

Microcrystalline cellulose (MCC, d_{10} = 11.59 μm, d_{50} = 45.35 μm, d_{90} = 108.0 μm) was used as the solid powder, purchased from Guangda Technological Development Co., Ltd. (Shandong, China; batch No. 201406030, GD-SD). De-ionized water was self-made and used as the binder.

Set-up and granulation procedures

A specially constructed lab scale HSWG (SHK-4, Xi'an Runtian Pharmaceutical Machinery Co., Ltd., Xi'an, China) was used in this study. The stainless steel working vessel was replaceable. The geometrical parameters of the three vessels are listed in Table 2. A replaceable three-bladed impeller made of stainless steel was centrally located on the base of the vessel. Each blade of the impeller was identical and had a leading edge inclined by 15°. A chopper was located on the sidewall. The rotational speeds of the impeller and chopper were controlled by PID controllers and could be fine-tuned from 300 to 1200 rpm and from 450 to 2900 rpm, respectively.

The MCC powders were dry mixed for 1 min at an impeller speed of 500 rpm and a chopper speed of 500 rpm. The binder solution was then added into the working vessel over 5 min using a peristaltic pump (BT00-100 M, Baoding Longer Precision Pump Co., Ltd., Baoding, China). After addition, the agglomerate was wet massed (i.e., the wet massing) at an impeller speed of 1000 rpm and a chopper speed of 1000 rpm. At the end of the granulation process, the mixture was discharged and transferred into an oven for drying at 60 °C for 3 h.

A vibration screen with nine standard sieves (ZNS-300, Beijing Kingslh Technology Development Co. Ltd., Beijing, China) was used to separate the raw granules into three parts: lumps, granules, and fine powders. The raw granules that could not pass through the

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