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Optimization of critical quality attributes in continuous twin-screw wet granulation via design space validated with pilot scale experimental data

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ABSTRACT

In this study, the influence of key process variables (screw speed, throughput and liquid to solid (L/S) ratio) of a continuous twin screw wet granulation (TSWG) was investigated using a central composite face-centered (CCF) experimental design method. Regression models were developed to predict the process responses (motor torque, granule residence time), granule properties (size distribution, volume average diameter, yield, relative width, flowability) and tablet properties (tensile strength). The effects of the three key process variables were analyzed via contour and interaction plots. The experimental results have demonstrated that all the process responses, granule properties and tablet properties are influenced by changing the screw speed, throughput and L/S ratio. The TSWG process was optimized to produce granules with specific volume average diameter of 150 μm and the yield of 95% based on the developed regression models. A design space (DS) was built based on volume average granule diameter between 90 and 200 μm and the granule yield larger than 75% with a failure probability analysis using Monte Carlo simulations. Validation experiments successfully validated the robustness and accuracy of the DS generated using the CCF experimental design in optimizing a continuous TSWG process.
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1. Introduction

Wet granulation is a key unit operation of solid dosage drug manufacturing process. This unit operation is used to improve granule properties such as size, flowability, dissolution rate, bulk density, compressibility and API uniformity by adding liquid granulation binder to raw materials. In addition to the pharmaceutical manufacturing industry, this technique is popularly adopted in many other industries including foods, detergent and fertilizers. Traditionally, batch granulation techniques have been employed in production of pharmaceutical granules (Crooks and Schade, 1978; Hemati et al., 2003; Liu et al., 2013, 2016; Liu and Li, 2014a,b). Recently, as the continuous manufacturing concept is introduced and discussed, implementation of a switch from batch granulation to continuous granulation has received attention. Continuous granulation has the advantage of high volume production with reduced equipment footprint, and control strategies which enable reduced process development time (Seem et al., 2015). Among the continuous wet granulation methods, twin screw wet granulation (TSWG) is well-suited for pharmaceutical processes due to its process stability, flexible scale up, short residence time, and controlled throughput (Keleb et al., 2004; Plumb, 2005; Vervaet and Remon, 2005; Vercruysse et al., 2012). During continuous TSWG, as the granulation liquid and powder materials are added into the equipment, the blend is mixed and conveyed through the barrel by specific screw elements, which allow separation of granulation mechanisms such as nucleation, layering growth and agglomeration, consolidation and breakage along the length of the barrel. Although TSWG has been investigated extensively as an individual unit operation, research on how TSWG works in integrated from-powder-to-tablet manufacturing is still relatively immature.

In order to optimize a process and improve manufacturing efficiency, it is critical to understand the effects of the formulation and process variables on the granule and tablet properties. Screw design has been shown to have a significant effect on granulation

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mechanisms and subsequent granule properties. Conveying elements with longer pitch were found to reduce the compaction of granules and the number of large agglomerates (Keleb et al., 2004). By using different screw elements, Djuric and Kleinebudde (2008) reported that the kneading blocks led to an almost complete agglomeration of lactose, while conveying and combing mixer elements resulted in smaller granules by comparison. The influence of process parameters such as screw speed, powder feed rate and liquid-to-solid ratio on the granule properties has also been investigated by researchers (Dhenge et al., 2010; Djuric and Kleinebudde, 2010; Thompson and Sun, 2010; Mu and Thompson, 2012; Vercruysse et al., 2012; El Hagrasy et al., 2013). It was found that increasing screw speed reduced the granule residence time and fill level, resulting in a small reduction in the size of granules (Dhenge et al., 2010). Under some circumstances, lower screw speeds can generate higher torque values due to greater screw filling and higher screw speeds at the same throughput can reduce torque due to increased conveying capacity (Thompson and Sun, 2010). Higher material feed rate at fixed screw speed increases the screw fill level and produces granules with low porosity and high strength with longer dissolution time (Djuric and Kleinebudde, 2010). Contrary to screw speed, increasing material feed rate leads to an increase in motor torque (Vercruysse et al., 2012). Liquid to solid (L/S) ratio (ratio between liquid flow rate and solid blend flow rate) has been widely acknowledged to be the most important factor regarding granule properties in TSWG. Several researchers reported that the average granule size increases with increasing L/S ratio (Mu and Thompson, 2012; El Hagrasy et al., 2013). Furthermore, El Hagrasy et al. (2013) observed that the granule size distribution (GSD) is switched from bimodal to mono-modal as L/S ratio increases regardless of the size of the input material, and hypothesized that the bimodal GSD is attributable to the method of binder addition. In TSWG, binder addition is performed by direct injection through a liquid inlet port, which forms a concentrated wetted area. Insufficient distribution of liquid binder results in coexistence of large wetted agglomerates and ungranulated fines (El Hagrasy et al., 2013).

While granule properties have been well studied, the influence of formulation and granulation process variables on tablet properties has been less discussed. Djuric and Kleinebudde (2008) evaluated the effect of three screw configurations comprised of conveying elements, combing mixer elements and kneading elements on tablet tensile strength. Their results showed that the conveying elements produced the most porous granules which yielded tablets with the highest tensile strength. The kneading elements produced the densest granules resulting in tablets with the lowest tensile strength, and combing mixer elements produced tablets with moderate tensile strength. Vercruysse et al. (2012) evaluated the effect of six process variables on tablet properties including tensile strength, friability, disintegration time, and dissolution profile and concluded that the quality of the tablet can be optimized by adjusting the number of kneading elements, the barrel temperature and the binder addition method during continuous TSWG. In addition to the process variables, Monteyne et al. (2016) also investigated formulation parameters such as binder type, binder concentration, and drug-binder miscibility and reported that the process variables interact with formulation parameters on affecting the tablet quality produced via TSWG.

As a significant component of the quality by design (QbD) principles, design of experiments (DoE) has been used to study the granule properties via TSWG (Kumar et al., 2016a,b; Monteyne et al., 2016). The use of DoE allows for testing a large number of factors simultaneously and precludes the use of a huge number of independent runs when the traditional step-by-step approach is used. Currently there are very few studies using a design of experimental approach to investigate the process outputs and tablet properties via continuous TSWG. In the current study, three process variables of screw speed (100–300 rpm), throughput (5–100 g/min) and L/S ratio (10%–70%) were systematically investigated to understand their effect on process outputs, granule properties and tablet properties using a central composite face-centered (CCF) experimental design method. Regression models for critical quality attributes (CQAs) of granule and tablet properties were developed. The TSWG process was optimized to produce specific granule properties and a design space (DS) was built based on volume average granule diameter and the granule yield using Monte Carlo simulations.

2. Materials and methods

2.1. Materials

The experimental data set used in this work was collected by Merck & Co., Inc. (Kenilworth, New Jersey, USA). The materials used for granulation were (material information, weight percentage in formulation): API (15%), microcystalline cellulose (Avicel PH 102, FMC, 16%), lactose monohydrate (312 impalpable, Foremost Farms, 16%), hydroxypropyl cellulose (Klucel EXF, Ashland, 2%), Croscarmellose sodium (FMC, 6%), Calcium carbonate (Innophos, 43.75%), Polysorbate 80 (Tween 80, Sigma Aldrich, 0.75%). For the tableting experiment, magnesium stearate (Mallinckrodt, 0.5%) was used as lubricant. During granule residence time (RT) determination, brown Opadry powder was used as tracer substance. Deionized water was used as the liquid binder.

2.2. Methods

2.2.1. Design of experiments

The central composite face-centered (CCF) experimental design was used to optimize and evaluate main effects, interaction effects and quadratic effects of the process variables on the process responses, CQAs of granules and tablets. A three-factor, three-level design was used because it was suitable for exploring quadratic response surfaces and constructing second order polynomial models for optimization. The independent factors and dependent variables used are listed in Table 1. The low, moderate and high levels of each independent factor were selected based on the results from the preliminary experiments. For the response surface methodology (RSM) involving CCF design, a total of 17 experiments were designed as shown in Table 2. This design is comprised of the three replicated center points, the set of points lying at the center of each surface and the corner of the cube defining the region of investigated parameters. The experimental design and data analysis were carried out using MODDE (V11.0.1, Umetrics, San Jose, CA). The following non-linear quadratic mathematical model was adopted to fit the experimental data of all process responses, granule properties and tablet properties:

$$Y = a_0 + a_1x_1 + a_2x_2 + a_3x_3 + a_{12}x_1x_2 + a_{13}x_1x_3 + a_{23}x_2x_3 + a_{11}x_1^2 + a_{22}x_2^2 + a_{33}x_3^2 \quad (1)$$

Where, Y is a measured response associated with each factor level combination; a_0 is an intercept; a_1 to a_{33} are regression coefficients calculated from the observed experimental values of Y; and x_1, x_2 and x_3 are the coded levels of independent variables. The terms of x_1x_2, x_1x_3, x_2x_3, and x_i^2 (i = 1–3) represent the interaction and quadratic terms, respectively.

2.2.2. Preparation of raw materials

The powder amounts of 5 kg for each experiment were blended in a 20-L Bohle blender for 10 min at 25 RPM to ensure

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