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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.

Graphical Abstract

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Keywords

Continuous twin screw wet granulation; Design of experiment (DoE); Monte Carlo simulation; Design space

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, Cherif et al., 2003; Liu, Wang et al., 2013; Liu and Li, 2014; Liu and Li, 2014; Liu, Yoon et al., 2016). 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, Rowson 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, Vermeire et al., 2004; Plumb, 2005; Vervaet and Remon, 2005; Vercruyssen, Córdoba Díaz 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 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, Vermeire et al., 2004). By using different screw elements, Djuric et al. (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, Fyles et al., 2010; Djuric and Kleinebudde, 2010; Thompson and Sun, 2010; Mu and Thompson, 2012; Vercruysse, Córdoba Díaz et al., 2012; El Hagrasy, Hennenkamp 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, Fyles 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, Córdoba Díaz 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, Hennenkamp 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, Hennenkamp 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 et al. (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, Alakarjula et al.,

2016; Monteyne, Vancoillie 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%), microcrystalline 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 ($i=1, 2, 3$) 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 minutes at 25 RPM to ensure homogenous mixing. The GSD of the primary ungranulated mixture was determined through image size analysis (Sympatec QicPic). The average granule diameter, fines, yield and oversized fractions of ungranulated mixture are 102.8 μm , 11.1%, 88.9% and 0%, respectively.

2.2.3 Twin screw granulation and drying—Granulation experiments were carried out in a co-rotating twin screw granulator (16 mm Prism Euro lab TSG, Thermo Fisher Scientific, Karlsruhe, Germany) having length to diameter (L/D) ratio of 25. The Thermo 16-mm screw barrel is comprised of 5 sections among which $3 \times 30^\circ$ kneading elements are used in the middle of the second section and conveying elements are used for all remaining sections. The screw configuration was kept constant for all experiments in this work. The material blend was fed into the first section of the barrel using a gravimetric loss-in-weight twin screw feeder (K-PH-CL-24-KT20, K-Tron Soder, Niederlenz, Switzerland) and the granulation liquid of deionized water was injected into the beginning of the second section by a controlled calibrated Masterflex peristaltic pump and silicon tubings connected to a 0.9 mm nozzle. The wet materials were intensively mixed by the kneading blocks in the second section and transporting conveying elements in following sections, and finally discharged from end of the fifth section of the twin screw granulator. The barrel jacket temperature was pre-heated and controlled at 25°C during the experiment. DoEs given in Table 2 were implemented. After the experiment was started, 3 minutes were allowed before sampling to ensure that the granulation process reached the steady state where the motor torque (Y_1) values reached relatively constant value. After granulation, the granules were placed in a tray and dried at room temperature for 24 hours. The dried granules were milled in a Quadro Cone Comill (model 193) at 3450 rpm using screen of 700 microns for further flowability measurement and tablet compaction.

2.2.4 Granule residence time and torque—Impulse response technique was used to determine the RT, and brown Opadry powder was used as a tracer. When the granulation process reached a steady state as indicated by a constant torque value, 5 grams of brown Opadry powder were introduced to the granulator powder feed port. A stopwatch was used to measure the residence time (Y_2) by sight. Time was started when the Opadry powder was added to the granulator feed port and stopped when the first brown granules were spotted exiting the barrel, which is the shortest granule residence time. The stopwatch was started again and stopped until the granules exiting the barrel returned back to white to record the longest granule residence time. The RT of granules was defined by average of measured shortest and longest residence time. The process response of torque was measured online by built-in probe, which was recorded directly from the TSG panel every 5 seconds. The torque values after reaching a steady state were used for calculation of average value.

2.2.5 Granule size distribution—A QicPic Particle Characterizer (SympaTec, Clausthal-Zellerfeld, Germany) was used for online measurement of GSD and volume average granule diameter (Y_6). The camera was installed at the exit of the extruder. Being an image analysis based size measurement tool, the results generated by QicPic camera are in number distribution of granules in the image taken and are then transferred into volume fraction based GSD for further analysis. The volume average granule diameter and relative width (Y_7) of GSD are calculated according to the following equations

Volume average granule diameter

$$\bar{D}_v = \frac{\sum_i f_i d_{pi}}{\sum_i f_i} \quad (2)$$

Relative width of GSD

$$RW = \frac{D_{v,90} - D_{v,10}}{D_{v,50}} \quad (3)$$

Where $\bar{D}_v$ is the volume average diameter of granules; d_{pi} is the geometrical mean of i th size interval; $D_{v,10}$, $D_{v,50}$ and $D_{v,90}$ are granule diameters at 10%, 50% and 90% percentages from the volume cumulative GSD; RW is the relative width of GSD.

The granule size range measured in this work is from 11 to 3650 microns. The granules with diameter smaller than 45 microns are defined as fines (Y_3) and the granules with diameter larger than 300 microns are defined as over-sized (Y_5). Hence, the yield (Y_4) of granules includes granules having diameter between 45 and 300 microns.

2.2.6 Bulk and tapped density—The granules were analyzed for bulk and tapped densities and Carr Index (Y_8). Granule samples of 5 grams were gently poured into a 50 mL graduated cylinder. The granule weight and volume were measured to calculate the bulk density. Using an automatic tapping machine (Quantachrome Dual Autotap), the cylinder was tapped 2000 times and the new volume was read to calculate the tapped density. The measured bulk and tapped density are shown in Table 3. Bulk and tapped densities were used to calculate the Carr Index.

$$Carr\ Index = 100 * \left(1 - \frac{Bulk\ Density}{Tapped\ Density}\right) \quad (4)$$

2.2.7 Carr Index—Carr Index is also called compressibility index. The compressibility index was used as an indirect method of predicting powder flow characteristics. Carr Index is calculated using the bulk and tapped densities to describe the granules flowability as shown in equation (4).

2.2.8 Tablet compaction and evaluation—Milled granules were weighted and dispensed in bottles. 0.5% (w/w) magnesium stearate was added as lubricant. The granules were lubricated 3 minutes at 46 rpm using a Turbula blender. The lubricated granules were used for tablet compaction on an RRDI Compaction Simulator using round flat-faced tooling at four compaction pressures of 100, 200, 300 and 400 MPa. Five tablets were compacted at each compaction forces for average calculation for each experiment. The target weight of each tablet was 300 mg. The tablet thickness, diameter, weight and hardness were measured on a SmartTest 50 semi-automatic tablet testing system. The tablet tensile strength (Y_9) is calculated according to the equation as follows:

$$T = \frac{2 \times 9.8 \times H}{\pi \times L_d \times L_t} \quad (5)$$

Where, H is the measured tablet hardness in unit kp; L_d and L_t are measured tablet diameter and thickness, respectively.

3. Results and discussion

In the study, a CCF DoE was applied to optimize the continuous TSWG process with input parameters of L/S ratio, screw speed and throughput. The observed responses for the 17 runs are given in Table 2. PLS regression models were fitted for process responses (torque and RT), granule properties (composition of fines, target granules, and oversized granules, volume average diameter, yield, relative width and Carr Index) and tablet tensile strength based on experimental data using MODDE software. Contour plots and interaction plots are used to study the influence of parameters of L/S ratio, screw speed and throughput and their interactions on process responses, granule properties and tablet tensile strength. Finally, the DS of L/S ratio, screw speed and throughput was determined to obtain a volume average granule diameter between 100 and 200 μm with a minimum 75% yield of granules. These specifications were obtained from the preliminary experimentation.

3.1 Evaluation of granulation process

3.1.1 Torque—The torque in a TSWG process is generated by the friction of granules against the screws and barrel wall and resistance to compression, which is an indication of extent of granule compaction within the barrel. The effect of screw speed and throughput on the torque at low, moderate and high L/S ratio is given in Figure 1(a). It can be seen that the effect of screw speed and throughput on the torque reversed as the L/S ratio increased from 10% to 70%. At moderate L/S ratio, the variations of screw speed and throughput did not significantly influence the torque. At high L/S ratio, increasing the screw speed resulted in decreased torque and increasing the throughput led to increased torque. This can be explained by the fill level and screw load which produce the torque (Dhenge, Fyles et al., 2010; Monteyne, Vancoillie et al., 2016). At high specific throughput, the resulting fill level was relatively high hence the screws had higher conveying load on them and high torque was observed. At high screw speed, the screw conveying rate is high generating low fill level hence low torque was observed. However, interestingly at low L/S ratio, it was found that increasing the screw speed resulted in increased torque and increasing material throughput

led to decreased torque. This phenomenon was also found by Kumar et al. (2014) which utilized $2 \times 30^\circ$ kneading discs in screw configuration and L/S ratio of 10% similar with this study. This is because liquid presence at the granule surfaces increases the ability of granules to transmit stress from the screws to the barrel. At low L/S ratio and fixed throughput, increasing screw speed improved liquid distribution on granule surfaces and produced higher torque. At low L/S ratio and fixed screw speed, increasing material throughput reduced liquid spreading resulting in lower torque.

The interaction plot has been used to display the predicted change in the response when one factor varies, and the second factor is set at both low and high levels, all other factors being set on their center. In the interaction plot, when the two lines are parallel there is no interaction between the two factors, whereas when they cross each other there is a strong interaction (Kumar, Vercruysse et al., 2014). The interaction terms of L/S*scr, L/S*thr and scr*thr were examined for analysis of their effects on the torque, as given in Figure 1(b). It is clearly shown that all the three interactions have significantly effect on the torque level. At high L/S ratio, the torque level decreased slowly by increasing screw speed due to the high conveying rate whereas at low L/S ratio, the torque increased sharply by increasing screw speed due to the enhanced liquid distribution. However, at high L/S ratio, the torque increased sharply by increasing material throughput whereas at low L/S ratio the torque decreased sharply by increasing material throughput. Especially at low L/S ratio, the adjustment of screw speed and throughput is actually adjusting the liquid distribution among materials, which indicates viscous forces between granules and the screws dominate the overall torque of the granulation process.

3.1.2 Granule residence time—Figure 2(a) shows the influence of screw speed and throughput on RT at low, moderate and high L/S ratios. The RT of granule increases significantly by increasing the L/S ratio from low to high level. This is explained, as the liquid content increases material flow is retarded. At all L/S ratios, increasing throughput resulted in a decrease of RT and increasing screw speed led to a decrease of RT, as expected (Dhenge, Fyles et al., 2010; Monteyne, Vancoillie et al., 2016). This is due to high throughput increased the fill level and produced high throughput force and less back mixing, reducing the RT. High screw speed increased the material conveying rate, which reduced the RT.

The effects of interactions between the three variables on RT are shown in Figure 2(b). At both high and low L/S ratios, the RT decreased at the same rate as throughput increased. Due to interaction between L/S ratio and screw speed (L/S*scr), an increase of screw speed resulted in more sharp decrease of RT at high L/S ratio than at low L/S ratio. However, due to interaction between screw speed and throughput (scr*thr), an increase of screw speed led to less decrease of RT at high throughput comparing to low throughput.

3.2 Evaluation of granule properties

3.2.1 Granule size distribution

3.2.1.1 Fines, yield and oversized fraction of granules: The effect of screw speed and throughput at low, moderate and high L/S ratios on fines is shown in Figure 3(a). Increasing

throughput resulted in an increase in fines fraction, in accordance with prior work (Dhenge, Washino et al., 2013). At constant screw speed and L/S ratio, high throughput means extra fine granules for certain amount of granulation liquid and short residence time for granule aggregation. At low L/S ratio, increasing screw speed contributed to spreading of small amount of liquid uniformly among materials and slightly reduced the fines fraction. However, at moderate and high L/S ratio, increasing screw speed resulted in an increase in fine fraction. This may be attributed to the breakage of large granules formed at high liquid level and shortened residence time caused by the high screw speed. As L/S ratio increased from 10% to 70%, the fines fraction dramatically decreased due to the high aggregation rate driven by the liquid (Fonteyne, Correia et al., 2015).

From Figure 3(b), it can be seen that the yield of target granules decreased as the screw speed increased for all levels of L/S ratio due to the shortened residence time for aggregation. At low L/S ratio, an increase in throughput slightly decreased the yield and at moderate and high L/S ratios, an increase in throughput resulted in an increase in yield. As analyzed in Figure 3(a) for the fine fraction, increasing throughput meant extra fines for low level of granulation liquid and therefore reduced the yield. However, for higher L/S ratios of 40% and 70%, sufficient liquid is present for aggregation, so increasing throughput improves granule aggregation and resulted in an increased amount of granules within the yield. From Figure 3(b), it was also observed that as the L/S ratio increased, the yield decreased. The additional granulation liquid mainly contributed to formation of oversized granules as shown in Figure 3(c) (Kumar, Dhondt et al., 2016). Comparing three figures of Figure 3(b), it can be concluded that all the three variables of L/S ratio, throughput and screw speed should be controlled at low levels for maximum yield of desirable granules.

From Figure 3(c), at low L/S ratio it is difficult to form over-sized granules. At higher L/S ratios, increasing throughput decreased over-sized granules as the granule residence time approached the drop penetration time. Increasing screw speed led to increased over-sized granules due to improved liquid spreading and granule growth by layering. Low screw speed also provides extended residence time for mixing and breakage. In summary, the L/S ratio played a critical role in reducing the fines and creating oversized granule. Maximum desirable granule yield was obtained at low L/S ratio.

Figure 4 summarizes the effect of interaction terms among screw speed, throughput and L/S ratio on fines, target granule yield and oversized fractions. From Figure 4(a), it is shown that the interaction between screw speed and L/S ratio ($L/S \times scr$) was indicated to have marginal effect on fines fraction while having significant effects on both target yield and oversized granules fractions. At low L/S ratio, the yield remained constant with changes in the screw speed while at high L/S ratio, the yield was decreased by increasing the screw speed with generation of oversized granules. Similarly, the interaction between L/S ratio and throughput ($L/S \times thr$) showed marginal effect on fines fraction but modest effect on target yield and oversized granule fraction. At low L/S ratio, both the yield and oversized fractions remained constant with changes in throughput while at high L/S ratio, the yield increased and the oversized fraction decreased by increasing the throughput. At high throughput, the yield and oversized fractions kept almost constant while at low throughput, the yield decreased

significantly and the oversized fraction increased significantly by increasing the screw speed.

3.2.1.2 Volume average granule diameter: Figure 5 shows the effect of screw speed and throughput at low, moderate and high L/S ratio by contour plots and interaction plots on the volume average granule diameter. From Figure 5(a), both screw speed and throughput had subtle influence on granule diameter at low L/S ratio, which is accordance with prior reports (Lee, Ingram et al., 2013). Lee et al. observed that variation in screw speed did not affect average granule diameter at low L/S ratio but at high L/S ratio increasing screw speed led to decreased average granule diameter. However, in this study, increasing screw speed led to a marginal increase in average granule diameter at moderate and high L/S ratios. This is because both the moderate and high L/S ratios in this work are sufficiently high to easily generate oversized granules at the beginning of granulator. High screw speed improved conveying rate and conserved those over-sized granules. At moderate and high L/S ratios, increasing throughput decreased average granule diameter (Dhenge, Fyles et al., 2010; Dhenge, Washino et al., 2013). It was also observed increasing the L/S ratio significantly increased the average granule diameter (El Hagrasy, Hennenkamp et al., 2013; Lee, Ingram et al., 2013; Lute, Dhenge et al., 2016).

From Figure 5(b), it was observed that the strongest interaction effect on average granule diameter occurred between L/S ratio and throughput. At low L/S ratio, the average granule diameter did not change with the throughput, which had been presented by analyzing the response contour plot. At high L/S ratio, increasing throughput resulted in a decrease in average granule diameter. The decreased average granule diameter can be attributed to the reduced moisture content caused by the increased throughput.

3.2.1.3 Relative width of granule size distribution: The relative width of GSD is an important quality attribute, which directly determines the yield of granules and needs to be studied. Figure 6 shows the effect of screw speed and throughput at low, moderate and high L/S ratios on relative width of GSD by response contour and interaction plots. At low and moderate L/S ratios, increasing screw speed resulted in an increase in relative width and broader GSD. This was attributed to the increased oversized granules and constant fine fraction as the screw speed increased as shown in Figure 3(a) and (c). At high L/S ratio, the granulation process was dominated by the high liquid content and the relative width was not affected by screw speed. Generally, narrower GSD was obtained by increasing the throughput due to the decreased oversized granules. From Figure 6(a), it was also observed that increasing L/S ratio resulted in a decrease in relative width (Dhenge, Fyles et al., 2010; El Hagrasy, Hennenkamp et al., 2013). Higher L/S ratio leads to a narrow mono-modal GSD.

From Figure 6(b), it is seen that the significant interaction existed between L/S ratio and throughput. At low L/S ratio, there is little change in relative width of GSD, while at high L/S ratio, increasing throughput resulted in an increase in relative width, producing much broader size distribution. This is caused by the high throughput introduced a high fine fraction of size distribution.

3.2.2 Carr Index—The Carr index is used as a measure of powder flowability. A critical advantage of wet granulation is to improve powder flowability. Overall, flowability is correlated with granule size, as expected. In Figure 7(a), it is shown that by increasing throughput, the flowability of granules was reduced by the appearance of large portions of fines (Dhenge, Washino et al., 2013; Monteyne, Vancoillie et al., 2016). At constant throughput and L/S ratio, increasing the screw speed improved flowability. Consolidation was enhanced by high screw speed with more frequency of collision between granules and between granules and barrel wall. In addition, from Figure 7(a), increasing L/S ratio significantly improved flowability of granules in agreement with prior studies (Meng, Kotamarthy et al., 2016).

From Figure 7(b), only the interaction between screw speed and throughput showed effect on flowability of granules. Increasing screw speed improved flowability at low throughput while reducing flowability at high throughput.

3.3 Evaluation of tablet properties

In this study, tablets were prepared under four compaction stresses of 100, 200, 300 and 400 MPa. The contour plots for the four fitted models are similar, so only the results of the tablet model at 200 MPa are shown in Figure 8. From Figure 8(a), it was observed that increasing screw speed resulted in high tablet tensile strength. This is because high screw speed reduced the fill level and granule residence time, which prevented granule breakage. The shortened residence time hindered the liquid spread and the large humidity granules formed at liquid addition section were quickly conveyed out of granulator. These granules experienced less consolidation and are deformable and porous. During tablet compaction, more interlocking bonding points are formed compared to dense granules, so producing tablets with enhanced tensile strength. On the other hand, decreasing screw speed increased fill level, under which consolidation and breakage occurred extensively and stronger granules were generated. The compressibility loss of granules resulted in decreased tablet tensile strength. Figure 8(a) indicated that increasing the throughput resulted in a decrease in tablet tensile strength. This is explained by the increased strength of granules at high throughput. Increasing the throughput led to increased fill and granules with high strength were formed with extensive consolidation and breakage (Dhenge, Fyles et al., 2010). In addition, from Figure 8(a), increasing L/S ratio generated increased tablet tensile strength. This is due to at high L/S ratio, existence of high liquid bridges produced deformable and porous granules, so producing high tablet tensile strength.

From Figure 8(b), it can be seen that the most significant interaction effect on tablet tensile strength occurred between screw speed and throughput. At high throughput, the tablet tensile strength remained almost constant by increasing screw speed. This indicated the limited effect of screw speed in changing the fill level at high throughput. At low throughput, increasing screw speed resulted in increased table tensile strength.

3.4 Optimization, design space and validation

Design space (DS) describes the relationship between the process inputs and the critical quality attributes (CQAs), and can help identify the critical process parameter (CPP) ranges

within which consistent CQAs can be achieved. ICH Q8 (CDER, November 2009) gives the definition of DS as: “Design space is the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.” DS defines the region within which the relevant quality attributes can be met.

Exploration of the DS was carried out using MODDE software. The considered CQAs are volume average diameter and the yield of desirable granules. The DS for the process parameters of screw speed, throughput and L/S ratio was determined based on applying a desired specification on volume average diameter ($90 < Y_1 < 200 \mu\text{m}$, aim: 150) and the yield of desirable granules ($Y_2 > 75\%$, aim: $> 95\%$). Firstly, “sweet spot” plots were constructed in terms of specifications for volume average diameter and the yield and presented in Figure 9. Blue regions show where the combination of process parameters satisfies only one CQA, and green regions (the sweet spot) show where both CQAs are satisfied. From the plots, it can be seen that a large portion of the potential operating space can satisfy both CQAs, especially at high throughput. The sweet spot plots were generated based on a regression deterministic model (Eq.5), which does not consider the model error and process uncertainty. A more realistic DS is created by performing Monte Carlo simulations based on regression models of volume average granule diameter and the granule yield considering the relative precision of the measured process parameters, constant factors, and model error. The DS is expected to be significantly smaller than the sweet spot plots. However, overall the CQAs are robustly met and fulfill the defined specification with negligible probability of failure, and the focus is process optimization.

In this study, the DS is presented in terms of probability of failure at each combination of the process parameters. A probability of failure level of 10% was selected, identifying the DS as the region where the predicted CQAs fulfilled the defined specifications with probability higher than 90%. A normal distribution with confidence level of 95% and confidence intervals of $\pm 5 \text{ rpm}$, $\pm 1 \text{ g/min}$ and $\pm 1 \%$ was selected to evaluate variability of screw speed, throughput and L/S ratio, respectively in the Monte Carlo simulation. 50,000 simulations were performed on each combination point. Firstly, optimization was performed on the basis of minimum DPMO (defects per million opportunities) with the following results: L/S ratio, 11%; screw speed, 500 rpm; throughput, 70 g/min. The DS (green color region in Figure 10) was calculated around the optimum set-point to the largest possible parameter range where all CQAs were predicted to meet the required specifications. From Figure 10, it can be observed that the largest DS for L/S ratio and screw speed was obtained at moderate throughput. It should be noted that the green area in sweet spot plots and DS are different. The green area in sweet spot plots means the granule specifications are fulfilled with probability of 100%, while in the DS it means 90% probability fulfillment of granule specifications. However, the area with failure probability higher than 50% are increasing with throughput in the DS (Figure 10), which is consistent with the sweet spot plots (Figure 9).

To validate the DS, four further experiments (see Figure 10) have been carried out, two of which were randomly selected inside the DS and the other two were randomly selected outside the DS. Table 4 shows the validation results of operating conditions, probability of

failure, the experimental CQAs. The two experiments within the DS with probability of failure of 9% and 2% generated volume average granule diameter and granule yield within the required range of specifications, while the two experiments performed outside the DS with probability of failure of 100% and 64% failed both volume average granule diameter and the granule yield specifications.

Within the design space, different operating conditions could generate the same qualified products. This provided potential for process optimization considering the cost difference on adjusting different operating variables. By setting the product CQA specifications, optimal operating variables could be calculated by solving optimization problem using the developed regression models. The built second order polynomial models could provide optimum solution. In addition, it was desired for continuous pharmaceutical manufacturing to adjust process variables without changing CQAs of product. This could be fulfilled through calculating other variables using the developed models.

4. Conclusions

In this study, the influence of process variables of screw speed, throughput and liquid to solid (L/S) ratio on granule and tablet properties by a continuous TSWG process was investigated using a central composite face-centered (CCF) experimental design. Regression models were developed to predict the process responses (motor torque, RT), granule properties (size distribution, volume average diameter, yield, relative width, flowability) and tablet properties (tensile strength). The effects of the three investigated process variables were analyzed using contour and interaction plots. The effect of screw speed and throughput on the torque reversed as the L/S ratio increasing from 10% to 70%. Increasing L/S ratio resulted in increased RT and increasing screw speed and throughput led to decreased RT. On optimizing the GSD, the L/S ratio played the most critical role where increasing L/S ratio reduced the fines fraction and increased the oversized fraction and maximum yield could be obtained at relatively low L/S ratio. With lower barrel fills from decreasing throughput or increasing screw speed, the flowability of granules was improved. However greater improvement was observed by increasing the L/S ratio. Increasing screw speed and L/S ratio generated tablets with increased tensile strength while increasing throughput resulted in decreased tablet tensile strength.

The TSWG process was optimized to produce granules with the specific volume average granule diameter of 150 μm and desirable granule yield of >95% based on the mathematical models developed here. The results showed that the quality of granules and tablets can be optimized by adjusting process variables of screw speed, throughput and L/S ratio during a continuous twin screw granulation process. Based on the understanding and knowledge gained, a DS based on volume average granule diameter (90–200 μm) and yield (>75%) was developed in terms of probability of failure using Monte Carlo simulations. Validation experiments have shown the reliability and effectiveness of the DS generated using the composite central-faced experimental design method in optimizing a continuous TSWG process. In summary, this work increased knowledge of the effect of TSWG process variables on the granule and tablet properties and could serve as basis for further developing mechanistic model for granulation process.

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(a)

(b)

Figure 1.

(a) Response contour plots showing effect of screw speed (X_1) and throughput (X_2) on the torque value (Y_1) at low (left), medium (middle) and high (right) level of L/S ratio (X_3); (b) Interaction plots showing the nonlinear quadratic effects of interactions between screw speed (X_1), throughput (X_2) and L/S ratio (X_3) on the torque value (Y_1).

(a)

(b)

Figure 2.

(a) Response contour plots showing effect of screw speed (X₁) and throughput (X₂) on the granule residence time (Y₂) at low (left), medium (middle) and high (right) level of L/S ratio (X₃); (b) Interaction plots showing the nonlinear quadratic effects of interactions between screw speed (X₁), throughput (X₂) and L/S ratio (X₃) on the granule residence time (Y₂).

(a)

(b)

(c)

Figure 3.

Response contour plots showing effect of screw speed (X_1) and throughput (X_2) at low (left), medium (middle) and high (right) level of L/S ratio (X_3) on: (a) fine fraction (Y_3), (b) the yield (Y_4) and (c) over-sized fraction (Y_5) of the granule size distribution.

(a)

(b)

(c)

Figure 4.

Interaction plots showing the nonlinear quadratic effects of interactions between screw speed (X_1), throughput (X_2) and L/S ratio (X_3) on: (a) fine fraction (Y_3), (b) the yield (Y_4) and (c) over-sized fraction (Y_5) of the granule size distribution.

(a)

(b)

Figure 5.

(a) Response contour plots showing effect of screw speed (X_1) and throughput (X_2) on the volume average granule diameter (Y_6) at low (left), medium (middle) and high (right) level of L/S ratio (X_3); (b) Interaction plots showing the nonlinear quadratic effects of interactions between screw speed (X_1), throughput (X_2) and L/S ratio (X_3) on the volume average granule diameter (Y_6).

(a)

(b)

Figure 6.

(a) Response contour plots showing effect of screw speed (X₁) and throughput (X₂) on the relative width (Y₇) at low (left), medium (middle) and high (right) level of L/S ratio (X₃);
 (b) Interaction plots showing the nonlinear quadratic effects of interactions between screw speed (X₁), throughput (X₂) and L/S ratio (X₃) on the relative width (Y₇).

(a)

(b)

Figure 7.

(a) Response contour plots showing effect of screw speed (X_1) and throughput (X_2) on the Carr Index (Y_8) at low (left), medium (middle) and high (right) level of L/S ratio (X_3); (b) Interaction plots showing the nonlinear quadratic effects of interactions between screw speed (X_1), throughput (X_2) and L/S ratio (X_3) on the Carr Index (Y_8).

(a)

(b)

Figure 8.

(a) Response contour plots showing effect of screw speed (X_1) and throughput (X_2) on the tablet tensile strength (Y_9) at low (left), medium (middle) and high (right) level of L/S ratio (X_3); (b) Interaction plots showing the nonlinear quadratic effects of interactions between screw speed (X_1), throughput (X_2) and L/S ratio (X_3) on the tablet tensile strength (Y_9).

Figure 9.

Sweet spot plots in terms of L/S ratio (X_3) and screw speed (X_1) at low (left), medium (middle) and high (right) level of throughput (X_2) defined with specification on the yield ($Y_4 \geq 75\%$) and the volume mean diameter ($90 \leq Y_6 \leq 200 \mu m$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article)

Figure 10.

Design space in terms of L/S ratio (X_3) and screw speed (X_1) at low (left), medium (middle) and high (right) level of throughput (X_2) defined with specification on the yield (Y_4 75%) and the volume mean diameter ($90 \leq Y_6 \leq 200 \mu\text{m}$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article)

Investigated formulation and process variables and levels in central composited face-centered experimental design

Table 1

Critical process parameters	Abbreviation	Low level (−1)	Medium level (0)	High level (+1)
X ₁ : Screw speed (rpm)	scr	100	300	500
X ₂ : Throughput (g/min)	thr	5	52.5	100
X ₃ : L/S ratio (%)	L/S	10	40	70
Process responses		specifications		Optimum
Y ₁ : Torque (N · m)		N/A		N/A
Y ₂ : Residence time (s)		N/A		N/A
Critical quality attributes		Specifications		Optimum
Y ₃ : Fines (%)		Y ₃ 10%		N/A
Y ₄ : Yield (%)		Y ₄ 75%		95%
Y ₅ : Over-sized (%)		Y ₅ 10%		N/A
Y ₆ : Volume average granule diameter (μm)		90 Y ₇ 200		150
Y ₇ : Relative width		Y ₇ 2		1.6
Y ₈ : Carr Index		Y ₈ 30		0
Y ₉ : Tensile strength (MPa)		Y ₉ > 2		N/A

Table 2

The central composite face-centered experimental design and experimental results

Run	Critical process parameters			Process responses		Granule properties						Tablet property	
	X ₁	X ₂	X ₃	Y ₁	Y ₂	Y ₃	Y ₄	Y ₅	Y ₆	Y ₇	Y ₈	Y ₉	
1	100	5	10	5.5	63.9	8.61	91.4	0	119.7	1.97	37.8		2.66
2	100	5	70	3.5	100	0.62	73.8	25.6	229.7	1.12	22.9		4.46
3	500	5	10	5.5	47.0	6.58	84.9	8.44	129.1	2.49	33.0		3.62
4	500	5	70	4.75	66.2	1.27	51.7	47	286.4	1.21	21.0		5.2
5	100	100	10	4	14.4	11.7	88.3	0	83.5	1.59	41.7		2.35
6	100	100	70	8	45.2	3.08	89.1	7.81	154.3	1.74	26.0		4.59
7	500	100	10	5.25	9.6	10.5	89.5	0	106.7	1.88	42.1		2.54
8	500	100	70	5	20.4	5.78	86.1	8.15	154.4	1.95	29.3		4.69
9	300	52.5	10	5	15.4	8.20	89.3	2.5	118.6	1.94	40.8		3.3
10	300	52.5	70	4	40.4	2.97	67.7	29.4	217.3	1.60	24.2		5.49
11	100	52.5	40	4.75	20.9	4.79	91.7	3.48	141.5	1.64	32.7		3.82
12	500	52.5	40	6.75	12.9	4.52	87.2	8.27	167.8	1.62	32.3		3.83
13	300	5	40	5.75	34.6	3.17	85.1	11.7	168.8	1.58	27.1		4.32
14	300	100	40	3.75	14.3	4.34	74.2	21.4	193.8	2.86	27.0		3.45
15	300	52.5	40	5.5	15.2	4.31	83.5	12.2	161.9	1.92	28.3		3.89
16	300	52.5	40	5.25	15.7	8.31	91.7	0	114.1	1.65	32.0		3.56
17	300	52.5	40	5.38	15.4	9.31	87.6	6.12	138.0	1.81	30.1		3.72

Table 3

The measured bulk density and tapped density

Mass (g)	Bulk Volume (mL)	Tapped Volume (mL)	Bulk Density (g/mL)	Tapped Density (g/mL)
4.58	9.8	6.1	0.47	0.75
5.11	9.6	7.4	0.53	0.69
5.03	9.7	6.5	0.52	0.77
5.93	10	7.9	0.59	0.75
4.04	9.6	5.6	0.42	0.72
5.00	9.6	7.1	0.52	0.70
4.08	9.5	5.5	0.43	0.74
4.71	9.9	7.0	0.48	0.67
4.50	9.8	5.8	0.46	0.78
5.19	9.5	7.2	0.55	0.72
4.86	9.8	6.6	0.50	0.74
4.74	9.6	6.5	0.49	0.73
5.27	9.6	7.0	0.55	0.75
5.18	10	7.3	0.52	0.71
5.20	9.9	7.1	0.53	0.73
4.81	9.7	6.6	0.50	0.73
5.00	9.8	6.9	0.51	0.73

Table 4

Validation experiments results for developed design space

Two-direction validation	Run	Conditions(X_1 (rpm)/ X_2 (g/min)/ X_3 (%))	Probability of failure	Experimental results (Y_4 (%) / Y_6 (μm))	If meet specifications (Y/N)
Selected inside DS	V1	300/5/25	9%	94.26/112.3	Y
	V2	300/52.5/25	2%	92.57/100.3	Y
Selected outside DS	V3	300/5/70	100%	75.09/213.8*	N
	V4	200/52.5/70	64%	73.98*/198.36	N