Solid dosage forms like tablets are the most popular and preferable delivery systems of drugs as their manufacture is simple, fast and economic (1). In the pharmaceutical industry, tableting operation involves several steps, including flow through the hopper, die filling and compaction (2). Thus, the materials, which are compressed into tablets, must possess adequate flowability, density, and compressibility. These requirements are particularly substantial during a high-speed tablet production where the dwell time is often short (3). Properties of the processed materials are to some extent interrelated to quality of final products such as stability, dissolution, disintegration, pharmaceutical availability and finally, bioavailability (4).

Most of the active ingredients have small particle size (100 µm or less) with irregular shape. They are highly cohesive and possess inadequate flowability due to presence of strong inter-particle interaction like electrostatic and Van der Walls forces (2, 5). Poor flow of pharmaceutical powders causes an undesirable process slump, thereby directly impacting the product uniformity. This inadequate flow can be modulated via agglomeration of powder particles in the presence of a liquid or solid binder which is known as size-enlargement or wet granulation process (6).

Particle engineering through wet granulation process provides opportunities for remedying poor pharmaceutical properties of drugs and thus facili-
tates the design of high quality products (4). Granulation process is carried out by spraying a granulating fluid onto the powder particles while they are agitated in low shear mixer, high shear mixer or fluidized bed. However, granulation in high shear mixer is widely used in the pharmaceutical industry because they provide high density and strong granules in a short processing time and less liquid binder’s consumption compared to low shear and fluidized bed (7). It does, however, need to be carefully controlled as the formulation can quickly progress from under- to overgranulated (8).

High shear granulation (HSG) is complex and multivariate process; the properties of the produced granules are highly sensitive to changes in process variables like impeller speed, massing time, amount of granulating fluid and its rate of addition. Consequently, it is important to investigate the effect of these critical parameters on the product properties (9, 10).

With respect to the Quality-by-Design (QbD) era, improvement of the quality of the product needs to identify and understand the manufacturing process variables that affect product quality. Moreover, it is critical to understand how those parameters affect the critical quality attributes (CQAs) of the final product (11).

Considerable endeavors have been made in the past few decades to provide a fundamental understanding of high shear granulation mechanism under varied process variables however, most of these studies have focused on the granule size as the criterion to characterize the fundamental of granulation processes (12). Not much effort has been reported in the literature on how critical granulation process parameters affect critical quality attributes of the intermediate (granules) and final product (tablets). This forms the motivation of our work.

Acetaminophen has been selected as a model drug in this study. It is a sparingly water-soluble drug which is administered in a high dose. It also exhibits poor flowability, poor compressibility and reduced plastic deformation (6). Acetaminophen is a substance which forms weak compacts giving rise to tablets which are prone to capping even at low applied pressure. Because of these properties, acetaminophen has been previously chosen as a standard to test the binding potential of excipients (13).

The binder is a key component in high-shear granulation and plays a crucial role in the formation of granules (14). Povidone was selected as a binder in our study as it provides harder granules with better flow properties than with other binders with lower friability and higher binding strength. Also povidone promotes the dissolution of the active ingredient (15). Furthermore, povidone K30 turned out to be the binders of choice for acetaminophen granulation with respect to crushing strength of the finished tablets (3).

The objective of the current work was to evaluate the effects of granulating liquid amount and wet massing time as critical processing variables in HSG process on CQAs of granules and corresponding tablet properties. A clear understanding of the correlation between HSG operating conditions and granule performance is expected to guide formulator in selecting suitable granulation process parameters for a robust manufacturing process using HSG.

MATERIALS AND METHODS

Materials

Micronized acetaminophen, USP, was supplied by JPI Co. (Riyadh, Saudi Arabia). Povidone (Kollidon 30) was purchased from BASF Co. (Ludwigshafen, Germany), croscarmellose sodium (Ac-Di-Sol) was kindly donated by FMC Bio-Polymer (Cork, Ireland) and magnesium stearate was purchased from Riedel-de Haën (Seelze, Germany). Distilled water was used as granulating fluid in all experiments.

Experimental design

High shear granulation process variables were evaluated on a qualitative basis using “trial and error” experimentation. The selection of process parameters used in preliminary investigation was based not only on the relative magnitude of parameters effects on granule characteristics, but also on the accuracy and precision with which these parameters could be controlled. It was observed that impeller speed and liquid addition rate were difficult to be controlled within the range of liquid level used (preliminary results are not shown). Therefore, it was important to keep the two variables constant to provide granules with reasonable quality. Moreover, qualitative screening resulted in the selection of granulating liquid amount (90-110 g) and wet massing time (1-5 min) as the two independent variables in our study. The impact of two process parameters on the granule and tablet attributes was studied using design of experiment (DoE) approach and a full factorial design (3²) was carried out. The levels of each variable are expressed by (-1) for the low level, (0) for the medium and (+1) for the high level as shown in Table 1. The full matrix of experiments is shown in Table 2. To determine the experimental error, the experiment at the center points was repli-
cated five times at different days (16). Also, all experimental batches were run and investigated in triplicate to decrease the possibility of error and increase the results confidence. The statistical analysis of the results was performed by analysis of variance (ANOVA) using statistical software package (Design Expert 9, USA).

Granules manufacture

Table 3 displays the quantitative composition of the formulation. Granulation process was carried out in high shear mixer/granulator (Hütting mycromix, BOSCH Packaging Technology, Schopfheim, Germany) with a 2L stainless steel bowl equipped with base mounted two blade impeller and vertically mounted a Christmas tree chopper design for deaggregation of larger agglomerates. The batch size was 500 g in all cases resulting in approximately 50% fill volume. Povidone was layered on the top of acetaminophen and pre-mixed for 2 min. Impeller speed was kept constant (300 rpm) through pre-blending and granulation process. Chopper speeds were run on high (3000 rpm) for pre-blending and for wet massing. For the wetting phase, the chopper speed was set to low (1500 rpm) (3). The blend was then granulated with the specified amount of water added at a rate of 90 g/min using a binary spray nozzle and atomizing air pressure through a tube attached to a pre-calibrated pump. The nozzle was placed 8 cm above the moving dry powder. After addition of granulating fluid, the system was run for pre-specified amount of massing time based on the design end point as per Table 2. The material was discharged from the granulator bowl and passed through 2 mm mesh screen. The wet granules were then arranged as a thin layer (thickness was about 5 mm) and dried in a hot-air convection oven at 60°C to a target loss on drying (LOD) value of 2%. The dried granules were then removed, passed through a 2 mm mesh screen and stored for subsequent evaluation and compression into tablets. Figure 1 shows the unit operations for granule manufacturing process.

Tablets manufacture

Acetaminophen granules, croscarmellose sodium and magnesium stearate were accurately weighed on an analytical balance. Mixture of acetaminophen granules and croscarmellose sodium was mixed for 10 min in Turbula mixer (type S27, Erweka, Apparatebau, Germany). The produced mixture was then mixed with the magnesium stearate for additional 2 min. Finally, the mixture was removed from the mixer and transferred to the hopper of the instrumented RoTap rotary tablet press (kg-pharma, Berlin, Germany). The tablet

<table>
<thead>
<tr>
<th>Experiment code</th>
<th>Water amount (g)</th>
<th>Wet massing time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
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<td>100</td>
<td>5</td>
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<tr>
<td>7</td>
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<td>1</td>
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<tr>
<td>8</td>
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<td>3</td>
</tr>
<tr>
<td>9</td>
<td>110</td>
<td>5</td>
</tr>
</tbody>
</table>
press was set up to produce four 10 mm flat tablets per cycle. The target tablet weight was adjusted to 350 mg. The produced tablets were collected and stored in tightly high density polyethylene (HDPE) container for subsequent investigation.

**Granules characterization**

Physical characteristics of the granules were investigated according to the United States Pharmacopeia (USP) methods (17).

**Particle size analysis**

Particle size and size distribution (n = 3) of the granules were measured by laser diffraction using Mastersizer 2000, with a Scirocco dry disperser (Malvern Instruments Ltd., UK). The samples (5-6 g) were air dispersed at an inlet air pressure of 1 bar and a feed-rate of 30%. Obscuration was maintained between 0.6 and 6% (18, 19).

**Blend density**

Bulk density (n = 3) of the particulates was determined using a 100 cm³ graduated cylinder. The granules were carefully poured into the cylinder up to a specified volume mark (V₀). The mass of the granules (m) was then determined and the bulk density (ρ_b) was calculated in grams per cubic centimeter (g/cm³) using Eq. (1).

\[
\rho_b = \frac{m}{V_0} \quad (1)
\]

The tapped density (n = 3) was measured using tap density equipment by subjecting the granules in the graduated cylinder to 400 "taps" from a height of approximately 2 cm. It was observed that, in all runs, 400 "taps" were enough to gain a constant occupation volume. The resulting volume after tapping (V_t) was measured to determine the tapped density (ρ_t) using Eq. (2).

\[
\rho_t = \frac{m}{V_t} \quad (2)
\]

**Compressibility index and Hausner ratio**

The compressibility index (CI) and the Hausner ratio (HR) can be calculated using measured values of bulk and tapped density using Eq. (3) and (4).

\[
CI = \left[\frac{(\rho_b - \rho_t)}{\rho_t}\right] \times 100 \quad (3)
\]

\[
HR = \frac{\rho_t}{\rho_b} \quad (4)
\]

**Flow properties**

The flowability properties for each granule batch were tested using the static angle of repose. Angle of repose is the internal angle between the surface of a pile of powder and the horizontal axis. It is the simplest and commonly used test for granule flowability.

Measurement of static angle of repose was performed by carefully pouring of granules through a dry funnel onto a circular plate to form a conical heap of granules. The funnel was fixed at approximately 4 cm above the heap of granules. At the end of the test, the angle between the surface of the powder heap and the surface of the plate is measured with measuring pin by aligning it parallel to the surface of the granules. Static angle of repose was calculated using Eq. (5).

\[
\tan(\alpha) = \frac{\text{height}}{(0.5 \times \text{base})} \quad (5)
\]

The mean of three determinations was taken as the angle of repose.

**Tablet evaluation**

**Weight uniformity**

Weight variation for 20 tablets was measured using (Erweka Multi-Check 5.1, Germany), the average tablet weight and standard deviation (SD) were recorded.

**Crushing strength**

The crushing strength was measured using (Erweka Multi-Check 5.1, Germany), the crushing strength of 10 tablets from each batch was recorded in kiloponds (kp). The mean and SD were recorded.

**Friability**

Tablet friability was determined according to USP38-NF33. Twenty tablets were randomly selected from each batch, weighed and placed into the friabilator (Erweka, TA3R, Heusenstamm, Germany) that was rotated at 25 rpm for 4 min. The tablets were then lightly brushed, reweighed to determine the loss in tablet weight. Friability was then calculated as percent loss in weight.

**Percent capping**

The tendency of the acetaminophen tablets toward capping was estimated using the friabilator described above. Upon dusting the tablets following friability testing, the number of tablets which displayed capping was recorded. Capping of the tablets was reported as the percent of tablets capped out of the total tested (20).

**Disintegration time**

Disintegration test was performed according to the USP38-NF33 requirements for immediate release tablets. Six tablets from each experiment were placed in a standard USP disintegration apparatus (Erweka, Germany) with 900 mL distilled water as the immersion fluid, adjusted at 37 ± 0.5°C. The basket rack assembly was allowed to
rise and lower at a constant frequency until the tablets were completely disintegrated and passed through the mesh. The disintegration time of each individual tablet was recorded in minutes. The mean and SD of the six tablets were calculated for each batch.

**Drug dissolution**

*In vitro* drug release was carried out according to the USP38-NF33 “Dissolution procedure” for immediate release dosage forms. Six tablets of each experiment were tested using the USP apparatus II method (Erweka, Germany); the paddle was rotated at 50 rpm. Dissolution was carried out in 900 mL phosphate buffer (pH 5.8 ± 0.05), maintained at 37 ± 0.5°C. Samples were withdrawn using 5 mL plastic syringe and replaced with a fresh medium at time interval of 15, 30, 45 and 60 min. The samples were filtered using 0.45 µm membrane filter into clean test tubes. One mL of the samples was removed from the test tube and diluted with phosphate buffer in 50 mL volumetric flask. The diluted samples were then analyzed for acetaminophen concentration using UV spectrophotometer (Shimadzu, UV-1800, Japan) at wavelength 243 nm. Lastly, the produced absorbance was converted into percent drug release using a calibration curve.

**RESULTS AND DISCUSSION**

**Influence of processing parameters on granule characteristics**

**Granule size distribution**

Table 4 lists the results of granule size distribution: it was observed that increasing the water amount from 90 to 110 g at the same time (5 min) results in increases of the granule size from 435 to 1017 µm, declines the % fines from 32.29 to 0% and reduction of distribution width from 3.386 to 0.94 (Fig. 2). These results are supported by the results of regression analysis (Table 5). Granulating liquid amount was found to be statistically significant on granule growth (p = 0.033) and granule median size (d50), (p = 0.029) and shows a clear trend. Also, granulating liquid amount has significant effect (p = 0.0006) on % fines which decreased in opposite trend to particle size with increasing water amount. The effect of water amount on granule growth and % fines can be explained by its effect on the degree of liquid saturation of the granules through the agglomeration process. Increasing water level resulted in increased liquid saturation of the granules, which in turn improved granule coalescence. Higher degree of liquid saturation is associated with more deformable granules and result in more free liquid at the granule surface, both of which increase the chance of coalescence upon granule collision resulting in an increase in granule size and a decrease in the amount of fines in the system. This concurs with previous studies (11, 21-24). The two-way interaction between granulating liquid amount and wet massing time were also found to be statistically significant to their effect on d50 (p = 0.056) and % fines (p = 0.009). Fig. 3(a), (b), (c) presents the contour plots showing the effect of tested parameters on granule mean size, d50 and % fines, respectively.

The water amount (p = 0.019), the wet massing time (p = 0.037) and the interaction between the two parameters (p = 0.034) were found to be statistically significant in terms of their effect on d10 and exhibits a clear trend as shown in Figure 3(d). The values of the d10 and the d50 of the system increase with increasing the water amount and wet massing time, therefore the granule size distribution gets narrower with increasing the both variables.

Figure 3(e) shows decreasing d90 with increasing wet massing times, this may be due to increasing wet massing times that can increase granule coalescence but at the same time can lead to enhanced breakage until a steady state distribution is reached (11). However, this effect is not statistically significant (p = 0.3811) and this may be due to the low impeller speed (200 rpm) that applied in our study.

Analysis of the width of granule size distribution (span) is critical as it has significant impact on granule flow, compressibility and segregation. A high span value indicates a wide size distribution of the system and vice versa. Wide size distribution is a result of (a) improper distribution of granulating liquid (b) formation of fragile granule (21, 22).

The water amount (p = 0.001) and its interaction with wet massing time (p = 0.006) were found to be statistically significant in terms of their effect on “distribution width” as shown in Figure 3(f); this can be explained by the fact that increasing the amount of granulating fluid leading to decrease the % fines in the system as a result of high liquid saturation and enhance the granulation process. It is noteworthy that % fines showed a good correlation (r² = 0.9147) with the distribution width values.

**Granule density**

An increase of water amount as well as massing time is leading to considerable increase of granule bulk density from 0.453 to 0.542 g cm⁻³ as shown in Table 4. Additionally, results of regression analysis showed that massing time (p = 0.009) has a sig-
Figure 1. Unit operation for granules and tablets manufacture

- Acetaminophen and Povidone
- Granulating liquid (water) with addition rate 90 g/min
- Dry blending stage: 300 rpm impeller, 3000 rpm chopper, 2 minutes
- Infusion stage: 300 rpm impeller, 1500 rpm chopper, 3 minutes
- Granulation stage: 300 rpm impeller, 3000 rpm chopper, 1-5 minutes
- Wet screen: 2 mm mesh screen
- Drying stage: Hot air oven at 60°C, LOD = 2%
- Dry screen: 2 mm mesh screen
- Ac-Di-Sol (10 min blending), Mg-st (2 min blending), 3D Turbula mixer
- Compression, 350 mg tablet, Rotary tablet press
- Granule evaluation, USP
- Tablet evaluation, USP
significant impact on bulk density followed by granulating liquid amount (p = 0.014) as shown in Figure 3 (g). Higher bulk density was observed when any of the two variables was increased, however there was no two-way interaction observed for this response. Longer massing time can result in a reduction in granule porosity and increased levels of consolidation and density by exposing the granules to high shear forces for a long period of time. Consolidation mechanism controls not only the level of air inside the granule but also controls the rate that binder eventually goes out of pores. This concurs with previous studies (11, 22, 23). In addition, water act as lubricant which decreases inter-particulate friction inside the granule thus improving movement of particle within the granule in response to densifying forces in high shear granulator (11). On the other hand, the tapped density of the granulation system showed the same trend for the influence of wet massing time (p = 0.003) and water amount (p = 0.014) (Fig. 3 (h)).

Granule flow

Values of the angle of repose of all batches are in excellent and good category according to the scaling of Carr, as presented in Table 4. In addition, values of compressibility indexes and Hausner ratios confirm the good flow properties of all runs. A flow property upon agglomeration process is improved as result of size enlargement, densification and reduction of % fines (21). The enhanced flow behavior in our system

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>% W/W</th>
</tr>
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<tbody>
<tr>
<td>Intragranule components</td>
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<tr>
<td>Acetaminophen</td>
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</tr>
<tr>
<td>Povidone 30</td>
<td>6</td>
</tr>
<tr>
<td>Distilled water</td>
<td>q.s.</td>
</tr>
<tr>
<td>Extragranular components</td>
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<tr>
<td>Croscarmellose sodium</td>
<td>2</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3. Formulation composition details.

Water amount 90 g, mean size 435.38 μm, % fines 32.29 % and span 3.386

Water amount 110 g, mean size 1017.439 μm, % fines 0 % and span 0.94

Figure 2. Effect of water amount on granule size distribution at 5 min massing time
Table 4. Results of granule and tablet evaluation with coded level of the processing parameters and their standard deviation.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>X₁</th>
<th>X₂</th>
<th>Y₁</th>
<th>Y₂</th>
<th>Y₃</th>
<th>Y₄</th>
<th>Y₅</th>
<th>Y₆</th>
<th>Y₇</th>
<th>Y₈</th>
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<tbody>
<tr>
<td>code</td>
<td>Water amount</td>
<td>Massing time</td>
<td>Mean size (µm)</td>
<td>d₁₀ (µm)</td>
<td>d₅₀ (µm)</td>
<td>d₉₀ (µm)</td>
<td>Percent Distribution</td>
<td>Bulk density (g cm⁻³)</td>
<td>Tapped density (g cm⁻³)</td>
<td>Compressibility index (%)</td>
<td>Hausner ratio</td>
<td>Angle of repose (°)</td>
<td></td>
</tr>
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<tr>
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</tr>
<tr>
<td>9</td>
<td>1</td>
<td>1</td>
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<td>598.117</td>
<td>971.573</td>
<td>1511.562</td>
<td>0</td>
<td>0.94</td>
<td>0.542 ± 0.0057</td>
<td>0.633 ± 0.0120</td>
<td>14.37</td>
<td>1.16</td>
<td>31.35 ± 0.13</td>
</tr>
</tbody>
</table>

X₁, X₂: independent variables, Y₁-Y₁₁: granule responses, Y₁₂-Y₁₇: tablet responses.
is mainly attributed to increased granule size and reduced % fines with little contribution of granule density. It was observed a high correlation between granule flow with the granule size ($r^2 = 0.9752$) and % fines ($r^2 = 0.9729$) while low correlation between granule flow and granule density ($r^2 = 0.8928$). Overall, variation in flow behaviors of the granules results from differences in granule characters like granule size, shape, density, and surface modification caused by granulation process (21). In addition, regression analysis showed that the granule flow was significantly improved ($p = 0.026$) by the increase in the granulating liquid amount due to a reduction in % fines and size enlargement as shown in Figure 3 (i). Wet massing time did not have a measurable effect on granule flow, there is no two-way interaction observed for this response. Also, amount of granulating liquid has a significant effect on compressibility indexes ($p = 0.033$) and Hausner ratios ($p = 0.037$).

### Influence of processing parameters on tablet characteristics

#### Tablet weight uniformity

Results of weight uniformity and its standard deviation (SD) are presented in Table 4. Data of weight uniformity were acceptable for all runs; SD was less than 2 indicating acceptable flow behavior for all granulation systems. Uniformity of tablet weight was significantly ($p = 0.041$) impacted by the amount of granulating liquid with little effect ($p = 0.703$) of wet massing time - Figure 4 (a). Values of SD were significantly reduced (1.9 to 1.1) by increasing the amount of granulating liquid as a result of improving granule flowability. Angle of repose values showed a good correlation ($r^2 = 0.9848$) with the SD of tablet weight uniformity.

#### Tablet crushing strength

Maximum hardness values provided from compression of all batches were used to analyze the compressibility characteristics of the granules. Results of regression analysis (Table 5) showed that maximum tablet hardness was significantly decreased by increasing the wet massing time ($p = 0.014$) and water amount ($p = 0.025$), respectively, as shown in Figure 4 (b). This suggests that low level of this parameter provides highly compressible granule. Reduction of granule compressibility by increasing the two processing parameters can be attributed to their effect on granule density. The

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### Table 5. Regression analysis data for $3^2$ full factorial experimental design, parameters estimate and their p-values.

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<th>Variables code</th>
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<th>$Y_4$</th>
<th>$Y_5$</th>
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<td>-0.69 (0.016)</td>
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<td>27.16 (0.546)</td>
<td>100.50 (0.037)</td>
<td>22.20 (0.673)</td>
<td>-40.01 (0.381)</td>
<td>-3.83 (0.033)</td>
<td>-10 (0.2019)</td>
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<tr>
<td>AB</td>
<td>131.24 (0.051)</td>
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<td>150.23 (0.056)</td>
<td>101.67 (0.103)</td>
<td>-6.60 (0.009)</td>
<td>-5.3 (0.0062)</td>
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<td>-0.20 (0.178)</td>
<td>-0.13 (0.571)</td>
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<td>19.44</td>
<td>14.31</td>
<td>83.31</td>
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<td>-11.67 (0.016)</td>
<td>2.8 (0.002)</td>
<td>-0.402 (0.0001)</td>
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<tr>
<td>B</td>
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<td>-0.38 (0.014)</td>
<td>-0.38 (0.207)</td>
<td>-4.17 (0.283)</td>
<td>2.07 (0.011)</td>
<td>-0.175 (0.0005)</td>
</tr>
<tr>
<td>AB</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
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</table>

- A: water amount; B: wet massing time; significant at $p < 0.05$. 

---
Figure 3. Contour plots showing the influence of water amount and wet massing time on granule characteristics.
reduction of tablet hardness of denser granules is explained by reduction of fragmentation and/or deformation of those granules through the compression cycle (25). A high correlation \( r^2 = 0.9954 \) between granule density and tablet hardness was observed. On the other hand, as the two processing parameters increased, the granule density increases, porosity decreases in turn and compressibility is reduced. Reduction of granule porosity resulted in a decrease in granule fragmentation, which leads to reduction in granule compressibility. The reduced compressibility of high density and less porous granules has been reported by several authors (11, 23-25).

**Tablet friability and percent capping**

The results of tablet friability and % capping for all experiments are given in Table 4. It can be seen that increasing the water amount (90-110 g) in the granulation system at the same massing time (3 min) results in a significant reduction in the values of friability and % capping, 2.62 to 0.04% and 35 to 0%, respectively. The tablet friability and % capping were found to be significantly \( p = 0.012 \) and \( p = 0.016 \), respectively) affected by amount of granulating liquid. An inverse relationship between water amount and tablet friability as well as % capping was observed as shown in Figure 4 (c), (d). This may be attributed to enhanced granule cohesiveness and reduction of % fines upon increasing the water amount in the system. It was reported that an increase in granulating liquid results in stronger liquid bridges and capillary adhesion between granules (26). A high correlation between % fines, friability \( r^2 = 0.9131 \) and % capping \( r^2 = 0.9638 \) was observed.

**Tablet disintegration**

Table 4 reports the results of tablet disintegration time for all runs. Results show that disintegration time is significantly influenced by water amount \( p = 0.002 \) and wet massing time \( p = 0.011 \) and, in particular, an increase of the two experimental variables produced an increase in disintegration time - Figure 4 (e). However, the interaction between the two variables was no longer important. The effect of water amount and wet massing time on tablet disintegration time may be attributed to increased density of granule and, in turn, decreased granule porosity. A plot of disintegration time versus granule density shows a high correlation between the two attributes \( r^2 = 0.9005 \). It was reported that tablet disintegration is influenced by extent of agglomerate densification during the wet granulation process (27). Reduction of disintegration efficiency by the dense tablet was also reported (28).

**Tablet dissolution**

Table 4 displays the results of % drug release after 15 min dissolution. It was noted that the release of the drug was declined with increasing of both process variables. Regression analysis of tablet dissolution (15 min) is presented in Table 5. Values of % drug released were shown to be significantly influenced by the water amount \( p > 0.0001 \) and wet massing time \( p = 0.0005 \), respectively. It was observed that the two variables were inversely proportional to % drug release after 15 min as shown in Figure 4 (f). The % drug released in 15 min showed a high correlation with both granule density \( r^2 = 0.9913 \) and granule size enlargement \( r^2 = 0.9295 \), since the elevation of granule size and density leads to a reduction in drug dissolution rate. This indicates that granule erosion and disintegration is a more predominant mechanism for drug release in this case. The impact of each studied variables on the overall % drug release decreased as sampling time increased from 15 to 60 min (data not shown). The reported effect of water amount and wet massing time on drug dissolution is in agreement with the results of Ring et al. (10) and Badawy et al. (11). High level of processing parameters (i.e., high granulating liquid amount and long massing time) provides tablet with the unacceptable dissolution profile.

**Main effects of the factors**

Judging from the p-values presented in Table 5, water amount has the main impact on all granule characters. However, influence of wet massing time has a higher extent than water amount of their effect on bulk and tapped density. In case of tablet properties, granulating liquid amount has its own effect on tablet weight uniformity, friability and % capping. With the increase of liquid amount the SD of weight variation, friability and % capping have decreased. Both water amount and massing time have a negative impact on granule compressibility, tablet crushing strength and tablet dissolution after 15 min. On the other hand, the two process variables have a positive effect with respect of disintegration time.

**Interaction between the factors**

Two-way interaction between two independent variables means that a factor cannot provide the same effect on the response at various levels of the other factor (16). Results of regression analysis
showed that the significant two-way interaction between water amount and massing time appeared at all estimated granule parameters except bulk and tapped density, HR and CI (linear model). In case of tablet characteristics, there is no interaction between the process variables on all estimated tablet properties as the suitable model applied was linear.

Inter-dependence of physical properties

Comprehensive analyses of the granule physical properties allow studying correlations and inter-dependence of these properties with each other. A good correlation between % fines with mean granule size ($r^2 = 0.8067$) and distribution width ($r^2 = 0.9169$) were observed. As expected, a higher level...
of % fines resulted in a decrease of granule size and broad size distribution. This suggests one-to-one dependence of % fines with the other parameters. This is in concurrence with the finding by Pandey et al. (24). It was observed that interdependence between flow pattern with granule size enlargement ($r^2 = 0.9525$), % fines ($r^2 = 0.9892$) and granule density ($r^2 = 0.0.8519$) indicates that extent of flow pattern is governed by different factors. However, the flow property of our system is more likely to be impacted by particle size enlargement and % fines than granule densification, as shown by the value of $r^2$. Overall, the increase in granule size and decrease of % fines appeared to reduce the values of the static angle of repose as well as improve the flow pattern. In addition, the relationship between granule flow and uniformity of tablet weight suggested one-to-one dependence.

Interdependence of tablet hardness with granule densification ($r^2 = -0.9954$) was also identified. Granulation bulk density was found to negatively correlate with granule compressibility and, in turn, tablet crushing strength. Moreover, a high correlation between % fines with friability ($r^2 = 0.9131$) and % capping ($r^2 = 0.9638$) has occurred. Furthermore, a high correlation between granule density and disintegration time ($r^2 = 0.9005$) was observed. Also, both granule size and bulk density appeared to negatively correlate with % drug released in 15 min ($r^2 = 0.9913$) ($r^2 = 0.9295$), respectively.

**CONCLUSION**

Full factorial design $3^2$ of experiments was employed to explore the influence of granulating liquid amount and massing time as critical processing parameters on the critical quality attributes of granule and corresponding tablet. Analysis of variance (ANOVA) identified that the liquid amount has largest impact and displaying obvious trend as shown by higher parameter estimate of granule physical properties. However, both granule density and compressibility were found to be significantly impacted by wet massing time. In addition, granule compressibility was highly sensitive to processing parameters. Both process parameters show antagonistic effect on disintegration time and drug dissolution after 15 min. Moreover, one-to-one interdependence of granule physical characteristics with each other was identified and correlated. Ultimately, recognizing the quantitative correlation between critical process parameters and critical quality attributes for intermediate and final product is critical to enable QbD approach, as well as provide basis for adjusting the high shear granulation process to produce product of high quality.

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**Declaration of interest**

The authors report no declarations of interest.

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