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Initial moisture content in raw material can profoundly influence high shear wet granulation process

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ABSTRACT

The aim of this work is to demonstrate that uncontrolled initial moisture content in microcrystalline cellulose (MCC) can profoundly affect high shear wet granulation (HSWG) process. We show that granule tabletability is reduced by approximately 50% when initial moisture content in MCC increases from 0.9% to 10.5% while all other processing parameters remain unchanged. An important observation is that granule tableting performance deteriorates significantly when initial moisture content increases from 2.6% to 4.9%, which is considered normal variation in moisture content for typical MCC (3–5%). The deteriorated tabletability is largely caused by increased granule size. On the other hand, granule flowability improves continuously with increasing initial moisture content in MCC. The improved flowability is mainly a result of granule size enlargement. Clearly, moisture content of raw materials for a HSWG process must be carefully monitored and controlled to ensure a robust manufacturing process as required by the quality-by-design principle.

1. Introduction

It has been well recognized that feeding raw materials with varying physical properties to a fixed process is a key problem that leads to variable product quality (Rathore and Winkle, 2009; Yu, 2008). Among the key properties related to pharmaceutical processing, water content is of recognized importance (Kaerger et al., 2004; Khan et al., 1981; Nicolas et al., 1999). Controlling moisture content is particularly important for hygroscopic excipients and drugs because materials may experience a wide range of relative humidity during their life time. The moisture content of hygroscopic excipients may differ among manufacturers due to different sources of raw materials and manufacturing processes. Even materials from the same manufacturer may show significant batch to batch variations unless specifications for material releasing are tight. Moreover, the same batch of material may still contain different amounts of water if they are stored or processed in different environments. For example, hygroscopic materials (*e.g.*, polyvinylpyrrolidone and hydroxypropyl cellulose) may contain more water when they are stored at a high humidity environment (*e.g.*, a humid summer) than low humidity environment (*e.g.*, a dry winter). Consequently, their performance during processing may vary, resulting in poor reproducibility.

It is well known that the amount of water used for high shear wet granulation (HSWG) can profoundly influence properties of the granules, downstream processing, and quality of the final products (Ameye et al., 2002; Shi et al., 2010, 2011b). It is conceivable that different initial water content in raw materials may significantly influence the manufacturing process. We found that, within a very narrow range of granulation water levels (65–70%), properties of microcrystalline cellulose (MCC) granules prepared by HSWG process underwent drastic changes in properties, a sharp transition from an acceptable granule to an over-granulated state (Shi et al., 2010). We hypothesize that the variations in initial water content of the starting materials will significantly influence the physical properties of MCC granules in this critical granulation region.

We evaluated the manufacturability of MCC granules using powder tableting performance and flowability (Sun et al., 2009) and characterized key granule physical properties, including morphology, porosity, and specific surface area (SSA), for arriving at a clear understanding of the changes in the mechanical performances of the granulated powders. Such understanding will help formulation scientists to design robust manufacturing processes and employ

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suitable strategies to ensure reproducibility, as required by the quality-by-design (QbD) framework (Sun, 2009; Yu, 2008).

2. Materials and methods

2.1. Materials

A single lot of MCC (Avicel PH101, FMC, Philadelphia, PA) was used as a model compound. A batch of MCC powder was first completely dried in a vacuum oven (646 torr) at 60 °C for one day. The dried MCC (~250 g each) was immediately transferred into a series of relative humidity (RH) chambers and equilibrated at room temperature for at least two weeks before being processed by HSWG. The approximately 0% RH chamber was prepared using anhydrous calcium sulfate. The 21.6%, 52%, 75%, and 93% RH chambers were prepared using saturated aqueous solutions of CH_3COOK, $Mg(NO_3)_2$, NaCl, and KNO_3, respectively (Rumondor et al., 2009; Sun, 2008). The water content of MCC materials was determined based on the weight change relative to dried powder. After storage, the MCC powders contained 0.9%, 2.6%, 4.6%, 7.2%, and 10.5% water by equilibrating at 0%, 21.6%, 52%, 75%, and 93% RH, respectively.

Once removed from the RH chamber, 100 g MCC powder (equivalent to a 100 g dry powder) was immediately transferred into a lab scale high-shear granulator (1.7 L bowl volume, modified from a food processor, KitchenAid, two impellers, 1750 rpm). While the powder was agitated in the bowl, 65 g of distilled water was sprayed through a nozzle, placed 5 cm above the moving powder bed, at a rate of 25 g/min. After spraying was completed, the wet material was further kneaded for 5 min. The wet granule was then oven-dried at 60 °C overnight. Dried samples were stored in a 52% RH chamber at 23 ± 1 °C for 7 days before tableting and flow testing. The obtained granules were designated as MWG-X, with X corresponding to the initial moisture content in the starting MCC powders. For example, MWG-4.6 referred to the granules prepared with MCC containing 4.6% water.

2.2. Tableting performance

Compaction of the obtained granules was carried out with a linear compaction simulator (Presster, Metropolitan Computing Company, New Jersey, NJ) simulating a rotary tablet press (KORSCH XL100, 10-station) at ambient environment (23 ± 1 °C and ~53% RH). The corresponding linear speed, dwell-time, and tableting speed were 0.65 m/s, 20 ms, and 61,600 tablets/h, respectively. Round (9.5 mm diameter), flat-faced tooling was used to produce cylindrical tablets.

Immediately after ejection, tablet weight, diameter and thickness, and the diametrical breaking force were measured. Breaking force was determined using a texture analyzer (TA-XT2i, Texture Technologies Corp., Scarsdale, NY) at a speed of 0.01 mm/s with a 5 g trigger force. Tablet tensile strength was calculated from the maximum breaking force and tablet dimensions (Fell and Newton, 1970; Sun and Hou, 2008).

2.3. Granule flow behavior

Flow properties of all granules were measured ($n = 3$) using a ring shear-cell tester (RST-XS, Dietmar Schulze, Wolfenbüttel, Germany) at ambient environment (23 ± 1 °C and ~53% RH) (Kamath et al., 1993). The shear cell volume was 30 mL. Pre-shear normal stresses were 1, 3, 6, and 9 kPa. Yield-loci (shear stress versus normal stress) were determined using a procedure previously described (Shi et al., 2011b). All tests were performed immediately after the shear cell was filled with powders.

From each yield locus, unconfined yield strength (f_c) and major principal stress (σ_n) were obtained. Flow function profile of a sample was constructed by plotting f_c against σ_n (Schulze, 2008; Schwedes, 1996). At the same σ_n, lower f_c indicated better flowability. The ratio of σ_n to f_c is the flow factor (*ff*). A higher *ff* value corresponds to better flow properties.

2.4. Granule size distribution

Granule size distributions ($n = 3$) were characterized using a laser scattering particle size analyzer (Mastersizer 2000 with a Scirocco dry module, Malvern Instruments Ltd., UK). The applied inlet air pressure and feed rate were 1 bar and 30%, respectively. Obscuration was maintained between 0.6% and 6%.

2.5. Granule morphology

A scanning electron microscope (SEM, Quanta 200F, FEI, Hillsboro, OR) operated at 10 kV was used to monitor the granule morphology. Prior to SEM experiments, samples were sputter-coated with a layer of platinum.

2.6. Granule porosity

Granule pore size distribution ($n = 1$) was measured using a mercury intrusion porosimeter (MIP, Autopore IV 9500, Micromeritics, Norcross, GA) with intrusion pressure varied from 5 to 33,000 psi (Abell et al., 1999). The granule porosity was calculated as the ratio of the volume of intruded mercury at the highest pressure to the total envelope volume of the granules. Based on the granule pore size distribution curves, 5 μm was selected as the cut-off point between inter-granular and intra-granular pores (Shi et al., 2011b).

2.7. Granule specific surface area

Initially, granule specific surface area (SSA) was measured by nitrogen adsorption using the Brunauer–Emmett–Teller (BET) method (Tristar, Micromeritics, Norcross, GA) (Brunauer et al., 1938; Denoyel et al., 2007). However, SSA values obtained were low, in the range of 0.08–0.20 m^2/g. We therefore repeated measurements using krypton adsorption, which is more accurate for low SSA samples. Before testing, all samples were purged with a continuous stream of nitrogen gas at 30 °C for more than 1 h. Krypton adsorption was measured at multiple partial pressures (P/P_0) ranging from 0.05 to 0.20. The absolute values in measured SSA differed slightly between the nitrogen and krypton adsorption. We only report krypton SSA values in this work.

3. Results and discussion

3.1. Granule tableting and flow performances

Tabletability and flowability are the two most important powder properties that determine powder processibility in pharmaceutical industry. Inferiority in either property can cause failed tablet manufacturing. Tabletability is usually represented by a plot of tablet tensile strength as a function of compaction pressure (Joiris et al., 1998; Sun and Grant, 2001).

Granule tabletability deteriorates with increasing initial moisture content in the starting materials (Fig. 1). The tabletability of MWG-0.9 is the highest (Fig. 1). The tabletability of MWG-2.6 is slightly lower than that of MWG-0.9, but remains higher than 2 MPa when compaction pressure is ≥200 MPa. When initial moisture content is increased from 2.6% to 4.6%, tabletability drops sharply. Tablet tensile strength reaches 2 MPa only at the highest compaction pressure of 400 MPa for MWG-4.6. Had this granule been lubricated with magnesium stearate, the highest tensile strength would be lower than 2 MPa, which is the desired minimum strength

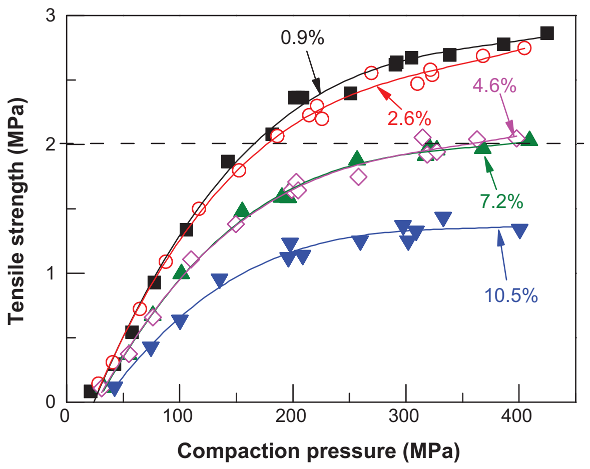

Fig. 1. Tabletability of granules prepared with MCC containing different amounts of water.

for tablets (Shi et al., 2010). This observation is troubling because the profound changes in granule properties take place while moisture content in MCC is in the typical range of 3–5%. Tabletability remains unchanged when initial moisture is increased from 4.6% to 7.2%, suggesting that the slightly changes in size, porosity, and SSA between MWG-4.6 and MWG-7.2 granules do not lead to observable change in tabletability. As such, it may be thought as a buffer zone when considering effects of initial moisture content on the granulation process of MCC. When the initial moisture content increases from 7.2% to 10.5%, another sharp drop in tabletability is again observed. The trend of change in tabletability is more clearly shown in Fig. 2 where tablet tensile strength at 300 MPa pressure is plotted as a function of initial moisture content in starting materials.

Variations in initial moisture content in starting materials also significantly affect flow properties of the resulting granules (Figs. 3 and 4). Increasing moisture content from 0.9% to 2.6% does not cause significant change in the flow factor of the granules. However, the flow factor increases significantly when the initial moisture content increases from 2.6% to 4.6% and then stays constant up to 7.2% (Fig. 3). When initial moisture content increases from 7.2% to 10.5%, granule flow factor again increases significantly. The overall trend is approximately a mirror image of that for tablet tensile strength (Fig. 2).

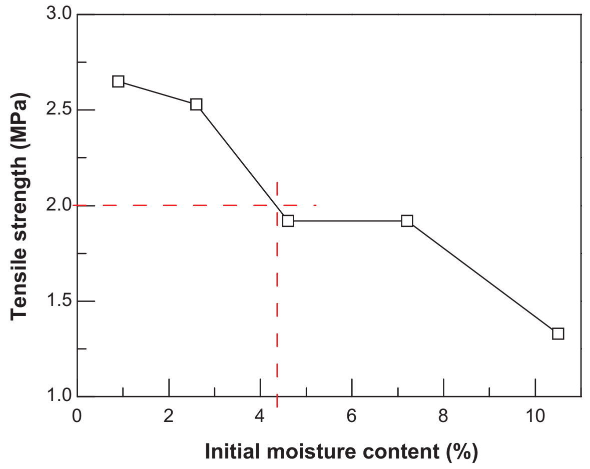

Fig. 2. Effect of initial moisture content of starting MCC on tablet tensile strength at 300 MPa compaction pressure.

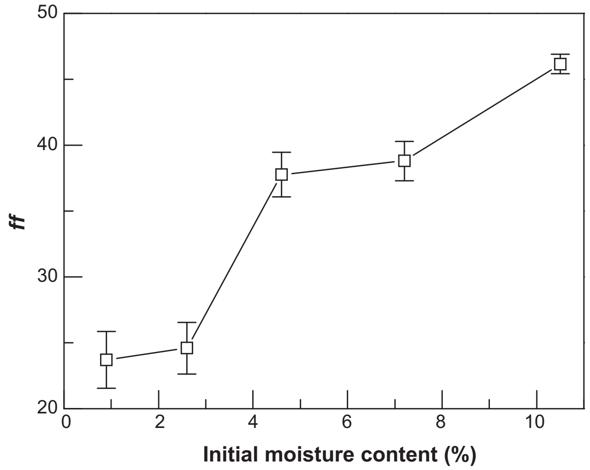

Fig. 3. Granule flow factor, at 10 kPa major principal stress, as a function of initial moisture content of starting MCC.

As shown by their much lower flow functions (Fig. 4), all of the granules have better flow properties than Avicel PH102, which exhibits the minimum flow properties acceptable for a successful high speed tableting process (Sun, 2010). Thus, all these granules are expected to present adequate flow for high speed tableting.

3.2. Granule physical properties

Powder tabletability and flowability are sensitive to granule morphology, size distribution, porosity, and specific surface area (Fell and Newton, 1971; Krycer et al., 1982; Shi et al., 2010, 2011b). Since the chemical and intrinsic mechanical properties of MCC are not expected to change among these granules, it is logical to examine these particulate properties for a better understanding of the observed effects of the initial moisture content on tabletability and flowability.

For MWG-0.9, most of the granules appear to be round in shape and smooth in surface texture without obvious pores (Fig. 5A), which indicates these granules are well consolidated and dense. This is in agreement with our previous work where 65% granulating water leads to smooth MCC granules when massing time is 5 min or longer (Shi et al., 2011a). These types of granules are hard and correspond to poor tabletability because they are more resistant to plastic deformation during compaction (Patel et al., 2011). Loose agglomerates (indicated by arrows shown in Fig. 5A) are present in MWG-0.9, suggesting the HSWG process at this point likely still

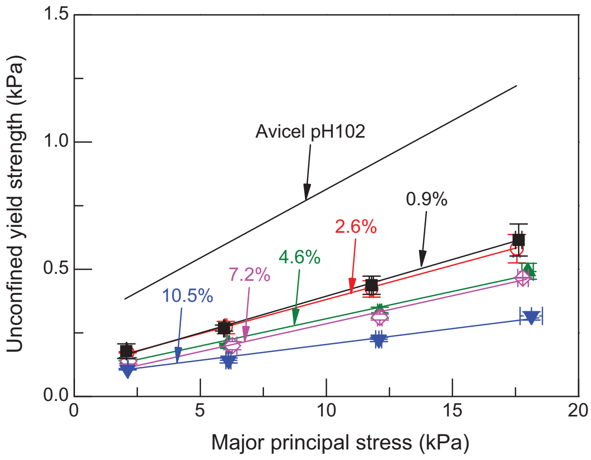

Fig. 4. Effect of moisture content of starting MCC on granule flow performance.

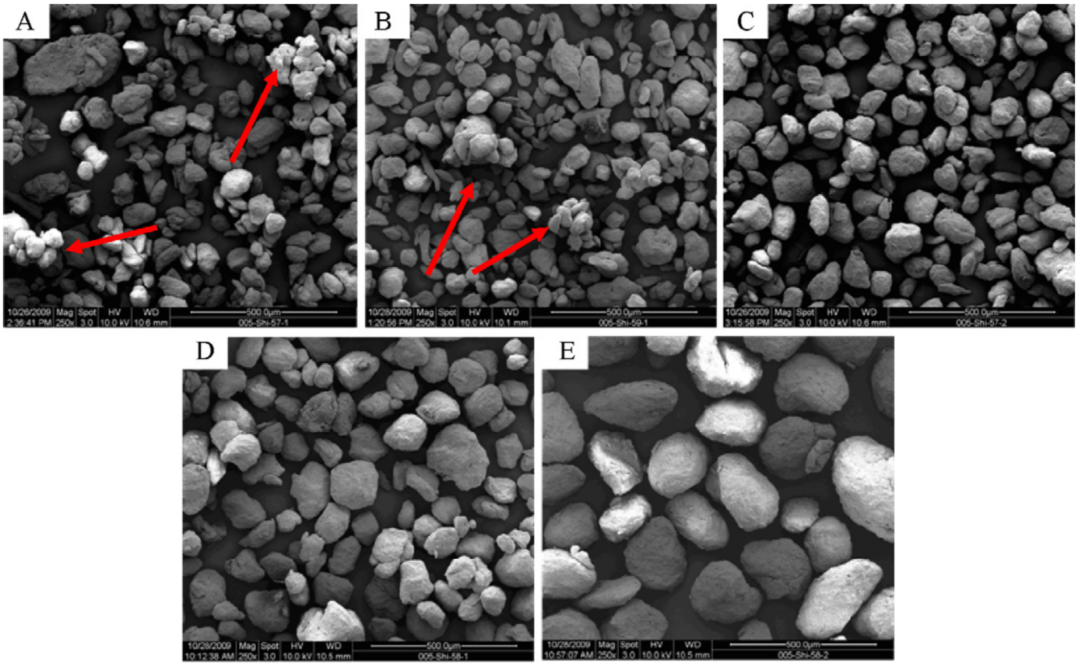

Fig. 5. Evolution of granule morphology with increasing initial moisture content of starting MCC. (A) 0.9%, (B) 2.6%, (C) 4.6%, (D) 7.2%, and (E) 10.5%.

remains in nucleation stage. These loose agglomerates are expected to be destroyed during the initial stages of compaction, which is dominated by particle rearrangement and slippage.

Compared with MWG-0.9, individual granules in MWG-2.6 are slightly larger but otherwise do not differ significantly in shape and surface texture (Fig. 5A and B). The granules also contain a small fraction of loose agglomerates (indicated by arrows shown in Fig. 5B).

Granules in MWG-4.6 are more uniform in size and loose agglomerates are essentially absent. With a further increase in initial moisture content from 4.6%, the only noticeable effect is larger granule size. As shown in this study, when the same process parameters are employed for raw materials with different moisture contents, resulting granules correspond to distinct stages of the granulation process. It is therefore not surprising that different granule properties are observed. An important ramification of this observation is the possibility of studying granulation kinetics in great detail by subjecting raw powders containing varying amounts of moisture to an identical granulating process. Initial moisture content in powders can be easily controlled by equilibrating them at different RHs.

The total water contents (initial water content + the granulating water) of the wet granules of MWG-7.2 and MWG-10.5 are 72.2% and 75.5%, respectively. The sharp increase in granule size for MWG-10.5 is in agreement with our earlier observation that granule size increases significantly when granulation water (for a dry MCC powder) was increased from 70% to 75% (Shi et al., 2010). The critical water content corresponding to a sudden increase in granule size may be explained by the liquid saturation theory in wet granulation (Badawy et al., 2000; Kristensen et al., 1985a,b). At a certain liquid saturation point, granule growth starts to be dominated by coalescence. This mechanism leads to rapid granule growth, which in turn causes a pronounced increase in granule growth rate (Iveson et al., 2001a,b). In accordance to the liquid saturation theory, our data suggest that the critical water saturation point for MCC PH101 lies in the range between 70% and 75% (Shi et al., 2010).

The qualitative SEM observation of granule size changes, induced by variations in initial moisture content in starting MCC, is supported by the quantitative size measurements using laser diffraction (Fig. 6). All granules show unimodal size distributions. The distribution curves shift continuously to larger size with increasing initial moisture content (Fig. 6). Granule size (d_{50}) increases from 99.4 ± 0.2 µm to 140.9 ± 2.3 µm when initial moisture content increases from 0.9% to 7.2%. However, d_{50} increases sharply to 292.2 ± 7.7 µm when initial moisture content is 10.5%. This corresponds to approximately 200% and 100% increase in granule size when compared to MWG-0.9 and MWG-7.2, respectively (Fig. 7). The increase in granule size explains the observed improvement in powder flowability.

It has been shown that intra-granular porosity is an important factor that affects powder compaction performance (Badawy et al., 2006; Johansson et al., 1995; Krycer et al., 1982). Since intra-granular porosity is one measure of the granule pore structure, its effects on granule properties and powder tableting performance are expected based on the Materials Science Tetrahedron (Sun, 2009). MWG-0.9 has the largest intra-granular porosity of 4.35%. This agrees well with our previous observation that intra-

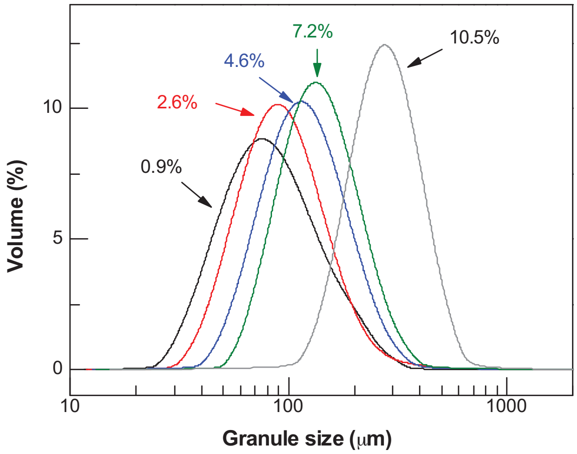

Fig. 6. Typical size distribution profiles of granules prepared with MCC containing different amounts of water.

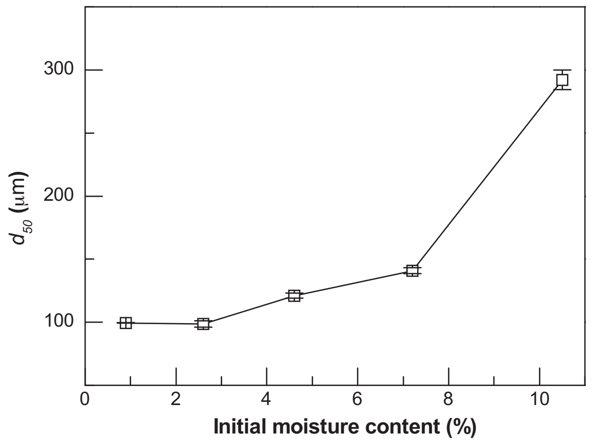

Fig. 7. Granule size as a function of initial moisture content of starting MCC.

granular porosity was less than 5% for MCC granules prepared with more than 65% water and 5 min of massing time (Shi et al., 2010, 2011a). Granule porosities are similar for all other samples (3.81%, 3.68%, 3.54%, and 3.54% for MWG-2.6, MWG-4.6, MWG-7.2, and MWG-10.5, respectively). This observation suggests that the liquid saturation point for MCC is near 67.6% (65% of granulating water + 2.6% of initial moisture in MCC). Before the saturation point is reached, more initial water leads to higher plasticity and easier pore shrinkage and elimination during collisions among the granules or between the granules and the impeller. However, when the saturation point is reached, granule plasticity is no longer affected by a slight increase in the water content, hence nearly constant intra-granular porosity.

Another important material property, SSA, decreases with increasing initial moisture content in MCC (Fig. 8). SSA of MWG-0.9 ($0.189 \pm 0.003\,\mathrm{m^2/g}$) is more than twice that of MWG-10.5 ($0.087 \pm 0.002\,\mathrm{m^2/g}$). The reduction in SSA is consistent with both the increase in granule size and reduction in granule porosity.

Effects of initial moisture content observed here are for pure MCC. Our results remind the importance of considering initial moisture in process development and manufacturing. This study also demonstrates how such effects can be systematically studied. However, real formulations contain multiple materials differing in physical, chemical, mechanical, and hygroscopic properties. An accurate depiction of the effects of RH and initial water content for individual formulations, therefore, requires dedicated studies.

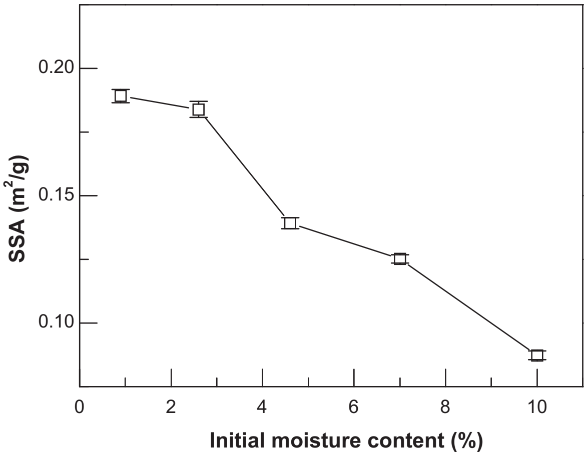

Fig. 8. Effect of the initial moisture content of starting MCC on granule specific surface area.

4. Conclusions

We have shown that the initial moisture content can significantly affect manufacturability of MCC granules by HSWG. Such effects are understood by systematically examining changes in granule structure (intra-granular porosity) and properties (size, shape, and SSA). Too much initial moisture (4.9% or higher) can easily lead the HSWG process to an over-granulated state for MCC even when the amount of granulating water is well controlled during manufacturing. This work, following the quality-by-design philosophy, highlights the importance of accounting the moisture content of raw materials, especially hygroscopic powders, in the HSWG process to ensure good batch-to-batch consistency in physical properties and manufacturing performance of granulated powders. Importantly, the consideration of moisture content should be made not only during manufacturing but also during formulation and process development to ensure successful scale-up and trouble-free manufacturing. This finding is expected to have widespread implications in pharmaceutical manufacturing because MCC is widely used in pharmaceutical products manufactured using the HSWG process.

Acknowledgements

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