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**Silicified microcrystalline cellulose based pellets and their physico-chemical properties**

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## **Abstract**

Silicified microcrystalline cellulose (SMCC), Prosolv® SMCC 50 was used as spheronization aid to manufacture pellets by extrusion and spheronization. Different ratios of SMCC to lactose were used to manufacture pellets using appropriate levels of water as liquid binder. Avicel PH101 based pellets were also manufactured for comparison of their physical properties. The ratio of liquid binder to spheronization aid was critical to produce pellets of desired size and shape. Extrudates composed of 20% aid could withstand only smaller spheronization force in order to be shaped into pellets. The successful products fulfilled the quality of pellets such as narrow size distribution and spherical in shape. The highest surface tensile strength was observed in pellets with equal ratio of lactose to SMCC while pellets having 20% aid disintegrated rapidly within 15 minutes. Furthermore, Prosolv® SMCC 50 based pellets possessed a stronger surface tensile strength when compared with Avicel PH101 based pellets. In conclusion, Prosolv® SMCC 50 has showed to be a good spheronization aid for extrusion and spheronization when used in the range of 20 to 80% content.

## Introduction

Pellets are intermediate products that are further processed into typically the multiple unit dosage forms as they are either compressed into disintegrating tablets or filled into hard gelatin capsules.

Pellets that are used pharmaceutically can be loaded with or without drug. Those pellets that are free of drug particles consist of a mixture of pharmaceutical excipients. These spherical cores with defined particle size are used as template where different drugs can be layered onto by conventional film coating technique. Depend on the size of the pellets different drug loading can be achieved. In addition, the pellets can be used as cushion to protect film coated granules during tablet process as well as modifying the tablet properties.

Extrusion and spheronization techniques are used commonly by the pharmaceutical industry to produce rigid pellets. They involve multiple stages to form pellet. Usually, it begins with dry mixing of the ingredients. Then wet massing of the homogenous blend using suitable liquid binder. It is followed by extrusion of the wet mass into cylindrical shaped powder agglomerates before transforming into spheres via a rolling mechanism known as spheronization.

Microcrystalline cellulose (MCC) is a purified and partial hydrolyzed cellulose derivative that is prepared by treating alpha cellulose (type I<sub>β</sub>) with mineral acids<sup>1</sup>. The alpha cellulose can be obtained from fibrous plant materials such as pulp. Apart from wood pulp as a source of cellulose, purified cotton linters from *Gossypium* species can also be used to produce MCC<sup>2</sup>. MCC is one of the widely-used aids in

pellet formation by extrusion and spheronization technique partly due to its water sorption and binding properties<sup>1</sup>. It tends to provide the wet mass with appropriate rheological properties and prevents phase separation throughout the processes by dominating the water movement in the plastic mass. Therefore, MCC-based pellets produced by extrusion and spheronization are presented with desirable properties such as good sphericity, low friability, smooth surface and high density. In spite of MCC's excellent characteristics, in certain cases MCC is not chosen for pellet production. For instance, some studies had showed the sorption of drug molecules onto the surface of MCC fibers as well as chemical incompatibility between MCC and various drugs. Also, MCC powders originated from different suppliers were found to alter physicochemical properties of pellets<sup>3-6</sup>. Thus, researchers have evaluated alternative spheronization aids such as k-carrageenan, powdered cellulose, blend of starch plus dextrin and even use of new grades of MCC, which is known as MCCII with the intention to overcome some of the limitations of standard MCC<sup>4, 7-8</sup>. Also, some researchers suggested mixing MCC and other excipients. For instance, Law and Deasy (1998)<sup>9</sup> incorporated hydrophilic polymers with MCC and they were able to achieve a higher yield and more spherical shape.

Co-processed excipients can be defined as a combination of two or more established excipients to provide an attractive mean to develop materials with high functionality<sup>10</sup>. Silicified microcrystalline cellulose (SMCC) is an example of co-processed excipient consisting of 98% MCC and 2% colloidal silicon dioxide<sup>11</sup>. The process of silicification changes the sorption property of SMCC when compares with MCC. It preserves the structure of SMCC from irreversible changes when exposed to

an environment of high relative humidity<sup>12</sup>. Also surface adsorption of certain drugs was reduced<sup>13</sup>. SMCC exhibits better flow property than MCC<sup>14</sup>. Improved flow behaviour of SMCC has resulted in a higher filled weight with similar filled weight variation by tamping encapsulation process into capsule<sup>15</sup>; supporting it as a suitable excipient to be directly filled into the capsule<sup>16</sup>. Furthermore, SMCC is found to be beneficial in direct compression and roller compaction processes as it provides good blending ability due partly to the presence of high degree of rough surfaces<sup>17</sup>. It also gives a greater binding capacity leading to formation of tough and compacted products with higher tensile strength and longer disintegration times but a low sensitivity to the presence of lubricants such as magnesium stearate<sup>18-22</sup>. SMCC with small particle size such as Prosolv<sup>®</sup> SMCC 50 is recommended for wet granulation in order to formulate into capsules, sustained release oral formulations or tablets. Unlike MCC, wet granulated SMCC based beads produced by high shear mixing have maintained their compactibility during tableting<sup>14</sup>.

The viability of producing pellets using Prosolv<sup>®</sup> SMCC 50 as an alternative spheronization aid by extrusion and spheronization is promising but literatures regarding pellets produced by this aid are sparse<sup>5</sup>. Prosolv<sup>®</sup> SMCC 50 possesses similar physicochemical properties as Avicel PH101 which is one of the most widely investigated spheronization aids<sup>14,23</sup>. Heng and Koo (2001)<sup>24</sup> produced pellets using 30% of different grades of MCC with lactose monohydrate as the other ingredient. Prosolv<sup>®</sup> SMCC 50 having a higher void volume but lower tapped density than Avicel PH101 was found to be less sensitive to variation of water added. This was because Prosolv<sup>®</sup> SMCC 50 could hold in more water within spaces of the polymer matrix

during pellet growth. Using only microcrystalline cellulose to produce pellets, Balaxi et al (2009)<sup>25</sup> have showed that Prosolv® SMCC 50 based pellets could be formulated with a wider range of water when compared to Avicel PH101. The observation was consistent with Heng and Koo (2001)<sup>24</sup>. In addition, Balaxi et al (2009)<sup>25</sup> examined the mechanical properties of their pellets and concluded that Prosolv® SMCC 50 based pellets had similar degree of porosity as Avicel PH101 based pellets. Nonetheless, the Prosolv® SMCC based pellets with low porosity (<14%) exhibited smaller tensile strength and they took much longer time to disintegrate than Avicel PH101 pellets.

In this work, pellets with different ratios of Prosolv® SMCC 50 as spheronization aid and lactose monohydrate as the hydrophilic component were produced by extrusion and spheronization technique. The amount of liquid binder used during the production of pellets and process conditions were examined. As the pellets were made from different ratios of lactose to SMCC, the characteristic of pellets such as size distribution, shape, tensile strength and density were examined. Also, the SMCC based pellets were compared with the Avicel based pellets.

## **Materials and Methods**

The spheronization aid used, Prosolv® SMCC 50 was obtained from Mendell, Penwest Company, USA. The liquid binder was freshly prepared distilled water. Granulac 230, a special grade of lactose monohydrate, was obtained from Meggle GmbH (Wasserburg, Germany).

## **Production of pellets**

Different batches of pellets were produced using blend of either Prosolv® SMCC 50 (SMCC) or Avicel PH101 (MCC) and Granulac 230 (lactose) via extrusion and spheronization technique. A total of 60 g of the ingredients were used to prepare pellets. The powders were pre-mixed in a planetary mixer (Model A901E, Kenwood Chef, UK) for 3 minutes at the speed setting of 3. Appropriate amount of freshly-prepared distilled water were added and the blend was mixed for further 10 minutes to create wet mass. The wet mass was then transferred to the radial extruder (Model 20 Extruder, Caleva Ltd, UK). The speed of the extruder was set to 30 rpm and the plastic mass was pushed through a screen with 1.0 mm die-holes. The extrudates were stored in an air-tight container for 30 minutes before spheronization using a bench top spheronizer (Model 120 GB, Caleva Ltd., UK). A 125 mm cross-hatch frictional plate was fitted to the spheronizer and appropriate spheronization speed was adjusted to spin the extrudates for 10 minutes. Typically speed settings of 2000 rpm and over were regarded as moderately high and those set to 1600 rpm and below were regarded as moderate. The freshly-prepared pellets were collected in a tray and left to dry at 50°C oven for at least two hours until a constant mass has reached. Table 1 lists the formulation components and the process conditions.

## **Determination of pellet size distribution**

The size distribution of the prepared pellets was determined with sieve analysis (EFL 2000 sieve shaker, Endecotts Ltd., UK) using a stack of British Standard sieves of  $\sqrt{2}$  progression between 0.25 and 2.00 mm. The pellets were added to the top sieve and



they were shaken for 10 minutes. The mass of the retained pellets on each sieve was determined to construct a frequency distribution. The percentage of fine (<0.50 mm) and coarse fractions (>1.40 mm) of the pellets were calculated. The median diameter ( $D_{50}$ ) and the interquartile range (IQR) were calculated using the cumulative percentage distribution. The percentage yield was determined based on the sieve fractions of 0.71 to 1.18 mm.

### **Determination of pellet shape**

The shape of the pellets was determined using an image analysis system (KS 400 version 3.0, Carl Zeiss Vision GmbH, Germany). Thirty pellets from 1.00 to 1.18 mm sieve fraction were selected randomly for shape determination. The pellets were placed under a pre-calibrated microscope (Model: Leitz Dialux 22, Ernest Leitz Wetzlar GmbH, Germany) and their images were captured using a digital camera (AxioCam MRc5, Carl Zeiss Vision GmbH, Germany). The area ( $A$ ), perimeter ( $P_m$ ) and Feret diameters of the pellets were measured and two shape factors, circularity and aspect ratios were calculated according to Podczec et al (1999)<sup>26</sup>.

### **Qualitative examination of pellet morphology**

The morphology of the pellets in the sieve fraction of 1.00 to 1.18 mm was viewed using high resolution scanning electron microscopy (SEM) (Hitachi S3000N, Hitachi High Technologies America Inc., USA) after the samples were coated with palladium and gold using a sputter coater (model SC7620, Quorum technologies, UK) for  $2 \times 10^5$  s at processing current of 18-20 mA as described by Puah et al (2014)<sup>27</sup>.

### **Determination of density of pellets**

The density of the pellets was determined using sieve fraction of 1.00 to 1.18 mm using a helium multi-pycnometer (Quantachrome Instruments, Boynton Beach, USA). Appropriate amount of pellets was placed into the micro cell sample holder. After the system was purged with helium in order to remove the adsorbed gases from the pellets,  $P_1$  (pressure of a fixed amount of gas in a reference volume) and  $P_2$  (pressure of a fixed amount of gas in sample cell) values were determined. The reference volume ( $V_R$ ) and the total volume of the system ( $V_C$ ) were calculated after calibration of the equipment using standard steel balls. The apparent volume of pellets ( $V_p$ ) is determined using the equation,  $V_p = V_C - V_R \left[ \left( \frac{P_1}{P_2} \right) - 1 \right]$  and the density of pellet is calculated by dividing the mass used by the calculated  $V_p$  value. The experiments were performed in triplicate for each batch.

#### **Determination of surface tensile strength of pellets**

The surface tensile strength of the pellets in the sieve fraction of 1.00 to 1.18 mm was determined using a mechanical testing instrument (CT-5 Engineering system, Nottingham, UK) fitted with a 5 kN load cell. The speed of the upper platen was set to  $1 \text{ mm} \cdot \text{min}^{-1}$ . The breaking loads of 30 pellets were obtained in order to calculate surface tensile strength using equation described by Shipway and Hutchings (1993)<sup>28</sup>.

#### **Determination of pellet disintegration time**

Fifty milligrams of pellets in the sieve fraction of 1.00 to 1.18 mm were placed in the disintegration instrument (Model: Erweka ZT4T; Apparatebau GMBH, Heusenstamm, Germany) fitted with a basket rack and mesh aperture of 0.42 mm. The basket rack

was immersed into the medium consisting of water at 30 dips.min<sup>-1</sup> and 37°C as previously described<sup>27</sup>. The time for the pellets to disintegrate was recorded. Test was repeated twice for each batch.

## **Results and discussion**

Different ratios of SMCC/MCC to lactose as well as SMCC/MCC to water were used to produce pellets. All the formulations chosen have been successfully made into pellets by extrusion and spheronization using moderately high spheronization speed except for the ratio of SMCC/MCC to lactose of 2 to 8. The extrudates are normally broken down into small and uniform fractions. This is achieved by the ongoing action of particle collisions with the wall or/and each other or/and fall back onto the rotating bed to create "rope-like" products and subsequently spheroids. Spheronization process can cause moisture loss<sup>29</sup> that reduces the plasticity of the particles. The effect is similar to the processing of under-wetted granules, which can lead to the formation of either deformed cylinders or dumbbell with plenty of fine fragments. The extrudates of P2E were dry and short in appearance. With only 20% of spheronization aid in the formulation to hold the compacted wet mass; the extrudates could not withstand the high centrifugal forces exerted during spheronization and were broken down into small fragments. By reducing spheronization speed but increasing the total amount of liquid binder, i.e. P2d, the batch also failed to form pellets. Although the extrudates of P2d appeared moist, these extrudates could not tolerate the applied spheronization force either. By lowering the spheronization speed further, P2a, P2b and P2c formed pellets and

there were not much powder sticking onto the spheronizer plate, indicating that the amount of liquid binder added was appropriate. Therefore, the moderate spheronization speed must be used for pellets with 20% or less of the aid.

Liquid binder acts as a lubricant and a plasticizer to help passing the wet mass through the extruder screen. It also aids shape deformation during extrusion and spheronization. The amount of liquid binder in wet massing is critical to the subsequent process. It is vital to achieve a uniform level of fluid distribution within the wet mass in order to form good quality pellets especially when limited amount of aid was used<sup>27</sup>. Table 1 shows that the amount of liquid binder required is closely related with the amount of Prosolv® SMCC 50 in the formulation, i.e. when the amount of SMCC increases, the ratio of water to SMCC decreases. However the total amount of liquid binder that has to be added into the formulation increases.

Although SMCC has a larger specific surface area than MCC<sup>30-31</sup>, water sorption process during wet granulation is not directly related to this property<sup>32</sup>. Hence, there is no noticeable difference in liquid binder requirement between Prosolv® SMCC 50 and Avicel PH101 during wet granulation<sup>33</sup>. In summary, for Prosolv® SMCC 50 despite possessing a slightly different composition in comparison to regular MCC, Avicel PH101, similar process conditions and liquid binder levels can be used across a wide the range of SMCC. Thus the pellet size enlargement adheres to the same principle as supported by Balaxi et al (2009)<sup>25</sup>.

## Size Distribution of pellets

In this study, apart from the spheronization aid, the other ingredient used is lactose monohydrate that has a moderate high aqueous solubility. Adding lactose is known to be beneficial for granulation process due to its tacky property. When looking at the size distribution for each batch (Table 1), the yields, coarse fractions and median diameters show more variations than other parameters. The model classes were mainly found in the range of 0.71 to 1.18 mm. Nonetheless, for the batches that have been processed under optimal conditions, the median diameters were close to 1.0 mm. Their fine and coarse fractions were low; typically less than 5%. Also, these batches achieved overall yields close to or above 80% within the required sieve fractions with relatively similar interquartile ranges. In general, median diameters of Prosolv® SMCC 50 based pellets tends to be marginally larger than the Avicel PH101 based pellets, indicating Prosolv® SMCC 50 is as good as Avicel PH101 for pelletization over a wide range of ratios apart from in its pure form as reported before<sup>25</sup>.

For the successful batches of pellets produced with SMCC to lactose ratio of 2 to 8 (i.e. P2a, P2b and P2c), the median diameters of the pellets were found to increase when higher spheronization speeds were used. Spheronization speed is known to play an essential role in controlling the size of the pellets. Wan et al. (1992)<sup>34</sup> reported that large pellets were produced when increasing spheronization speed. This observation was also supported by Hasznos et al. (1992)<sup>35</sup> where operating at a higher spheronization speed had increased the coarse fraction and mean diameters of the pellets. Although P2c was manufactured with a durable but higher

spheronization speed, an excessive amount of energy was used. The coarse fraction of P2c was over 10% when compared to the other batches (P2a and P2b), which were within the 5% limit.

Small changes in the level of liquid binder to SMCC were applied to batches with 40% (P4a, b, c) and 60% (P6a, b, c) SMCC. In general, increasing water level led to larger median diameters (P4a and P6a, Table 1) and variation in terms of yield was more prominent with P4 formulations due partly to the presence of less spheronization aid.

### **Shape factor and morphology**

The spherical shape of pellet provides good flow property while a low surface to volume ratio allows a uniform layer of coating to be deposited<sup>36</sup>. Aspect ratio and circularity were determined to estimate the shape of pellets. The mean aspect ratio and circularity values of the pellets were typically less than 1.3 and over 0.85, respectively (Table 1). Thus, the pellets produced were sufficiently round. The morphology of pellets were also examined using SEM confirming that the pellets formed were typically round with relatively similar surface textures regardless of the pellet components (Figure 1). Koo and Heng (2001)<sup>37</sup> had shown that the physical properties of pellets differed when various grades of MCC were used. Prosolv® SMCC 50 and Avicel PH101 powders possess similar size distribution and shapes<sup>11, 30, 38</sup>. Although silicon dioxide found on the particles' surface to make SMCC powder rough in appearance, surface textures of pellets were similar regardless of the type of aids.

Earlier works by Wan et al. (1992)<sup>34</sup> and Dua et al. (2011)<sup>39</sup> for instance, had showed that spheronization speed affected the shape of pellets. In our study, only one batch of pellets fell outside of the desired range, i.e. P2a. In this case, the total energy applied was not enough due to low spheronization speed used. There were many studies on regular MCC as aid, for example, Sinha et al. (2005)<sup>40</sup> reported that the pellets produced using lactose and Avicel PH101 met the desired sphericity. Our observations also confirm that Prosolv® SMCC 50 can produce round pellets down to 20% SMCC content and is non inferior to regular MCC, i.e. Avicel PH101. As Avicel PH101 based pellets were produced using same optimal conditions as the Prosolv® SMCC based pellets, A2 with the least amount of aid varied more in terms of size distribution and shape, thus, formulations become more sensitive to the amount of water at this level (Table 1).

### **Density of pellets**

Gas pycnometer is an equipment described in the pharmacopoeia to determine the density of solid material. With high diffusivity, helium gas is preferred over other gases. The particle density is derived after measuring the volume occupied by a known quantity of solid sample that is equivalent to the volume of helium displaced by the sample. This derived volume excludes the volume occupied by open pores but includes the volume of the sealed pores or pores inaccessible to helium gas. It has been widely used to determine density for processed pharmaceutical powder samples including those of the pellets<sup>41-42</sup>.

Density influences pellet transit along the gastrointestinal tract. A critical density range to achieve a delay in gastric emptying and tentatively prolonged release of

drug in the stomach from coated pellets was 2.4 to 2.8 g.cm<sup>-3</sup> <sup>41-42</sup>. The pellet densities produced with Prosolv<sup>®</sup> SMCC 50 or Avicel PH101 according to the conditions in this study are found in the close range of 1.4 and 1.5 g.cm<sup>-3</sup> (Table 1). The derived values are comparable to previous works using regular MCC<sup>40</sup>. Also, pellet densities are found to reduce gradually with increasing amount of the spheronization aid in the formulations (Figure 2). All the raw ingredients have similar true densities <sup>11, 38, 43</sup>. Our results were also comparable to those published earlier <sup>30, 44</sup>. Prosolv<sup>®</sup> SMCC 50 powder possesses a greater inter-granular porosity (calculated based on the true and bulk densities) than lactose<sup>11, 43, 45</sup>. It is also more elastic than standard MCC<sup>46</sup>. Hence, the pellets with higher Prosolv<sup>®</sup> SMCC 50 tend to exhibit a looser packing. As lactose is fairly soluble in water, small portion of the lactose molecules dissolve when they come in contact with water. This increases the cohesiveness of the powder mixture and thus enhancing the interaction between undissolved particles to form denser pellets.

The Avicel PH101 based pellets tend to exhibit higher densities than those of Prosolv<sup>®</sup> SMCC 50 based pellets when the content of the aid in the formulations is 50% and over (P5 vs. A5 and P8 vs. A8, Table 1). Buckton et al (1999)<sup>23</sup> has showed that pure SMCC powder possesses similar internal structure as its granulated form. This observation has indicated that the interaction among different functional groups such as OH and CH bonds were retained unlike standard MCC after exposure to the wet massing fluid (i.e. water) or drying process. This may partly explain the lower density values of the SMCC based pellets. Pellets produced with MCC/SMCC to lactose at the ratio of 2 to 8 were expected to be less dense. This is partly due to the



application of lower spheronization speed to densify extrudes that were generally weaker in nature. Also, small changes of the spheronization speeds and liquid binder levels close to the optimal conditions have resulted in similar density values as seen in pellets with 20 and 40 or 60% SMCC, respectively (Table 1).

### **Mechanical properties of pellets**

Both Prosolv<sup>®</sup> SMCC 50 and Avicel PH101 based pellets are considered rigid and strong with mean surface tensile strength ranging from 1 to 6 MPa and breaking load of 3 to 16 N (Table 1). Except for pellets with 20% spheronization aid (where the surface tensile strength values were less than 2 MPa and rapid disintegration times were observed), other pellets did not fully disintegrate in 45 minutes. This result is consistent with Puah et al (2014)<sup>27</sup> where pellets with 20% Avicel CL611 showed rapid disintegration times. As degrees of crystallinity of Prosolv<sup>®</sup> SMCC 50 and Avicel PH101 are higher than the modified forms of cellulose such as SMCCII, thus the disintegration times are anticipated to be longer<sup>44</sup>. For those pellets that did not disintegrate, the surface structures were more porous with pellets containing higher lactose content after exposure to the disintegration condition (Figure 3). This is accounted by a greater degree of material leaching from these pellets, especially due to loss of lactose which is soluble. Hence, the presence of either SMCC or MCC helps to keep the structure of the pellet intact. The pellets can potentially be useful for further development into modified release preparation loaded with drug. In general, Prosolv<sup>®</sup> SMCC based pellets were mechanically stronger than Avicel PH101 based pellets in terms of surface tensile strength and breaking load (Figure 4). Moreover, both sets of pellets exhibit similar disintegration profiles (Table 1), despite the fact

that the relative swelling capacity of SMCC powder was reported to be higher than MCC<sup>30</sup>. In contrast, Balaxi et al (2009)<sup>25</sup> showed that disintegration time for fluid bed dried pellets consisting of solely Prosolv® SMCC 50 was more than 5 hours which was doubled of their Avicel PH101 pellets. They deduced the differences in the disintegration times to the reduction in particle separation due to presence of silicon dioxide in SMCC. Also upon drying, the relaxation of the polymeric matrix chains has partly been hindered to prevent rapid disintegration of the pellets while the internal bonds are retained to preserve its mechanical property<sup>23</sup>.

As reported by Sousa et al. (2002)<sup>47</sup>, mechanical property of pellet is related to its physicochemical properties such as density. Weak pellets in terms of lower breaking load and surface tensile strength were observed in pellets with 20% spheronization aid (Figure 4). The surface tensile strength and breaking load of the pellets gradually increase and peak at equal ratio of aid to lactose and then decline. Lactose monohydrate that was used in this study is a crystalline material. It dissolves much more in water than MCC or SMCC. Dissolved lactose molecules can act as binder thus increases the cohesiveness of the agglomerate. Upon drying, these molecules recrystallize as solid bridges and give the hardness to the pellets. The presence of lactose, which is brittle in nature, has resulted in crack to pellets' surface under the applied stress with the exception of pellets that consist of 80% aid. Kruger et al (2013)<sup>8</sup> has showed that as lactose content (50-90%) in MCCII pellets increases, the pellets' tensile strength values decrease supporting our observations for pellets produced in the similar range. Also, a study done by Teixeira (2007)<sup>48</sup> has shown that lactose has a weaker tensile strength than SMCC dried powder compact. Thus, for

the pellets with less than 50% SMCC or MCC, the mechanical properties of pellets are dominated by property of lactose.

When the content of spheronization aid is higher than lactose, the surface tensile and breaking load also reduce gradually. Increase in liquid binder content during manufacture of pellets can result in pellets with stronger mechanical properties<sup>27, 47</sup>.

The pellets produced in current work employed different levels of water depending on the formulation components to form pellets of desired size and shape. As SMCC and lactose absorb or adsorb water molecules, the interaction between water molecules and these materials differ<sup>32</sup>. Lactose monohydrate and SMCC exhibit type 3 and 2 sorption isotherms, respectively. Upon sorption of water to the surface of SMCC, these particles swell (with a typical swelling volume of  $4.3 \text{ ml.g}^{-1}$ )<sup>30</sup> and the voids in this material are filled with the penetrating water molecules. The porous network of SMCC thus retains some of the water molecules within its gel matrix. On the other hand, adsorption of water molecules is minimal for lactose. Deliquescence of lactose occurs when it is placed in the environment with high relative humidity. It has been reported that every 5 grams of water dissolves approximately 1 gram of lactose<sup>43</sup>. Therefore, lactose and SMCC are competing with each other for water molecules. During the initial stage of water addition to the dried powder blend where water level in the powder blend is quite low, water molecules are likely to be greatly adsorbed onto SMCC. Upon further water addition to reach the optimal fluid level for the wet mass before extrusion, it also dissolves some of the lactose molecules in the powder blend. Formation of lactose solution also contributes to an increase in the overall moisture content within the wet mass. The interactions

amongst undissolved particles involve complex process where particle agglomeration is governed by several mechanisms such as Van de Waal force at close proximity, electrostatic interaction in the presence of water molecules. In our work, the percentage of water added is roughly doubled ranging from 20 to 80% SMCC/MCC of the dried blend (i.e. ~19 vs. ~43g of water), due to the proportional reduction of water ratio as SMCC/MCC content increases. Presumably the number of water molecules is reduced by approximately half in the formulations with 20% SMCC/MCC, but at this condition, liquid saturation must be attained for particles to agglomerate. Besides the proportion of undissolved particles is similar for all samples (less than 10% differences by mass based on lactose solubility as mentioned above) assuming lactose is the only dissolving species. Airaksinen et al (2005)<sup>32</sup> has described the phase transition of lactose monohydrate to anhydrous beta lactose when the former was exposed to water at high relative humidity followed by drying at high temperature. In addition, upon oven drying, pores within the pellets shrink due to partial removal of water molecules from the cellulose networks and recrystallization of dissolved lactose molecules occur. These processes can alter the physical properties of the pellets. Though water level is known to affect the mechanical properties of the pellets, the changes in level of added water in our case did not define the differences in the tensile strength behaviour.

## **Conclusions**

This work has successfully utilized Prosolv® SMCC 50 as a spheronization aid to manufacture pellets containing hydrophilic component, i.e. lactose monohydrate,

with a wide range of SMCC/lactose ratios using extrusion and spheronization. The products fulfilled the desired quality of pellets such as narrow size distribution and spherical in shape. Except when using low content of the aid (20% or less), pellets can be produced by moderately high spheronization speed. The ratio of liquid binder to spheronization aid is critical to form pellets of desired size and shape. The higher content of aid in the formulation, the lesser proportion of water to aid is required to form pellets, and better pellet shape with smaller median diameters were formed. Furthermore, the amount of aid affects density, surface tensile strength and disintegration profiles of the pellets. Mechanical properties of pellets were the highest at equal ratio of aid to lactose. Also, Prosolv® SMCC 50 based pellets exhibit stronger surface tensile strength when compared to Avicel PH101 based pellets. In summary, the study showed that Prosolv® SMCC 50 can be used as a good alternative aid to Avicel PH101.

#### **Declaration of interest**

The authors report no declarations of interest.

## References

- [1] Thoorens G, Krier F, Leclercq, Carlin B, Evrard B. Microcrystalline cellulose, a direct compression binder in a quality by design environment-- A review. *Int J Pharm* 2014; 473: 64-72.
- [2] Ohwoavworhua FO, Adalakun TA. Some Physical Characteristic of Microcrystalline Cellulose Obtained from Raw Cotton of *Cochlospermumplanchonii*. *Trop J Pharm Res* 2005; 4: 501-507.
- [3] Al-Nimry, S., Assaf, S., Jalal, Najib, N. Adsorption of ketotifen onto some pharmaceutical excipients. *Int J Pharm*, 1997; 149(1):115-121
- [4] Dukić-Ott A, Thommes M, Remon JP, Kleinebudde P, Vervaet C. Production of pellets via extrusion-spheronisation without the incorporation of microcrystalline cellulose: A critical review. *Eur J Pharm Biopharm* 2009; 71: 38-46.
- [5] Otero-Espinar FJ, Luzardo-Alvarez L, Blanco-Méndez J. Non-MCC materials as extrusion-spheronization aids in pellet production. *J Drug Del Sci Tech* 2010; 20: 303-318.
- [6] Verheyen P, Steffens KJ, Kleinebudde. Use of crospovidone as pelletization aid as alternative to microcrystalline cellulose: effects on pellet properties. *Drug Dev Ind Pharm* 2009; 35:1325-1332.

- [7] Almeida Prieto, S, Blanco Méndez, J, Otero Espinar, F. Starch–dextrin mixtures as base excipients for extrusion–spheronization pellets. *Eur J Pharm Biopharm* 2005; 59(3):511-521.
- [8] Krueger C, Thommes M, Kleinebudde P. Influence of storage condition on properties of MCC II-based pellets with theophylline-monohydrate. *Eur J Pharm Biopharm* 2013, 88(2):483-91.
- [9] Law, MFL, Deasy, PB. Use of hydrophilic polymers with microcrystalline cellulose to improve extrusion–spheronization. *Eur J Pharm Biopharm* 1998; 45(1):57-65.
- [10] Garg N, Dureja H, Kaushik D. Co-processed excipients: A patent review. *Recent Pat Drug Deliv Formul* 2013; 1: 73-83
- [11] Rowe RC, Sheskey PJ, Quinn ME. Cellulose, silicified microcrystalline. In: *Handbook of Pharmaceutical Excipients, Sixth editions*, Pharmaceutical Press, 2009: 139-141.
- [12] Kachrimanis K, Noisternig MF, Griesser UJ, Malamataris S. Dynamic moisture sorption and desorption of standard and silicified microcrystalline cellulose. *Eur J Pharm Biopharm* 2006; 64(3):307-15.
- [13] Steele DF, Edge S, Tobyn MJ, Moreton RC, Staniforth JN. Adsorption of an amine drug onto microcrystalline cellulose and silicified microcrystalline cellulose samples. *Drug Dev Ind Pharm* 2003; 29(4),475-87
- [14] Sherwood BE, Becker J. A new class of high functionality excipients: silicified microcrystalline cellulose. *Pharm Tech* 1998; 22: 183–194

[15] Felton LA, Garcia DI, Farmer R. Weight and weight uniformity of hard gelatin capsules filled with microcrystalline cellulose and silicified microcrystalline cellulose. *Drug Dev Ind Pharm* 2002; 28(4):467-72.

[16] Guo M, Augsburger LL. Potential application of silicified microcrystalline cellulose in direct-fill formulations for automatic capsule-filling machines. *Pharm Dev Technol* 2003; 8(1):47-59.

[17] Zeleznik JA; Renak J. High functionality excipients (HFE)-ProSolv SMCC as an effective strategy for generic drug formulation. *Tech Serv* 2005; 1-4

[18] Edge S, Steele DF, Chen A, Tobyn MJ, Staniforth JN. The mechanical properties of compacts of microcrystalline cellulose and silicified microcrystalline cellulose. *Int J Pharm* 2000; 200(1):67-72.

[19] Edge S, Steele DF, Tobyn MJ, Staniforth JN, Chen A. Directional bonding in compacted microcrystalline cellulose. *Drug Dev Ind Pharm* 2001; 27(7):613-21.

[20] Hentschel CM, Sakmann A, Leopold CS. Comparison of traditional and novel tableting excipients: physical and compaction properties. *Pharm Dev Technol* 2012; 17(6):649-53.

[21] Kachrimanis K, Nikolakakis I, Malamataris S. Tensile strength and disintegration of tableted silicified microcrystalline cellulose: influences of interparticle bonding. *J Pharm Sci* 2003; 92(7):1489-501.



[22] van Veen B, Bolhuis GK, Wu YS, Zuurman K, Frijlink HW. Compaction mechanism and tablet strength of unlubricated and lubricated (silicified) microcrystalline cellulose. *Eur J Pharm Biopharm* 2005; 59(1):133-8.

[23] Buckton G, Yonemochi E, Yoon WL, Moffat AC. Water sorption and near IR spectroscopy to study the differences between microcrystalline cellulose and silicified microcrystalline cellulose before and after wet granulation. *Int J Pharm*, 1999; 181(1): 41–47

[24] Heng PWS, Koo OMY. A study of the effects of the physical characteristics of microcrystalline cellulose on performance in extrusion spherulization. *Pharm Res* 2001; 18: 480 -487.

[25] Balaxi M, Nikolakakis I, Kachrimanis K, Malamataris S. Combined effects of wetting, drying, and microcrystalline cellulose type on the mechanical strength and disintegration of pellets. *J Pharm Sci* 2009; 98(2):676-89

[26] Podczek F, Rahman SR, Newton JM. Evaluation of a standardised procedure to assess the shape of pellets using image analysis. *Int J Pharm* 1999; 192: 123-138.

[27] Puah SY, Yap HN, Chaw CS. Production and Characterization of Pellets using Avicel CL611 as Spherulization aid. *Drug Dev Ind Pharm* 2014; 40: 418-424.

[28] Shipway PH, Hutchings IM. Attrition of brittle spheres by fracture under compression and impact loading. *Powder Technol* 1993; 76:23–30.

- [29] Hellén L, Yliruusi J, Kristoffersson E, Merkkü P. Process Variables of Instant Granulator and Spheronizer: Physical Properties of Granules, Extrudate and Pellets. *Int J Pharm* 1993; 96: 197-204.
- [30] Luukkonen P, Schaefer T, Hellén L, Juppo AM, Yliruusi J. Rheological characterization of microcrystalline cellulose and silicified microcrystalline cellulose wet masses using a mixer torque rheometer. *Int J Pharm* 1999;188(2):181-92.
- [31] Steele DF, Tobyn M, Edge S, Chen A, Staniforth JN. Physicochemical and mechanical evaluation of a novel high density grade of silicified microcrystalline cellulose. *Drug Dev Ind Pharm* 2004; 30(1):103-9.
- [32] Airaksinen S, Karjalainen M, Shevchenko A, Westermarck S, Leppänen E, Rantanen J, Yliruusi J. Role of water in the physical stability of solid dosage formulations. *J Pharm Sci* 2005; 94(10):2147-65.
- [33] Luukkonen P, Schaefer T, Podczek F, Newton M, Hellén L, Yliruusi J. Characterization of microcrystalline cellulose and silicified microcrystalline cellulose wet masses using a powder rheometer. *Eur J Pharm Sci* 2001; 13(2):143-9.
- [34] Wan LSC, Heng PWS, Liew CV. Spheronization conditions on spheroid shape and size. *Int J Pharm* 1992; 96: 59-65.
- [35] Hasznos L, Langer I, Gyarmathy M. Some Factors Influencing pellet Characteristics made by an Extrusion/Spheronization process Part I: Effects on size characteristics and moisture content decrease of pellets. *Drug Dev Ind Pharm* 1992; 18: 409-437.

- [36] Heng PWS, Wong TW, Chan LW. Influence of Production variables on the Sphericity of melt pellets. *Chem Pharm Bull* 2000; 48: 420-424.
- [37] Koo OM, Heng PW (2001). The influence of microcrystalline cellulose grade on shape and shape distributions of pellets produced by extrusion-spheronization. *Chem Pharm Bull (Tokyo)*, 49(11):1383-7.
- [38] Rowe RC, Sheskey PJ, Quinn ME. Cellulose, microcrystalline. In: *Handbook of Pharmaceutical Excipients*, Sixth editions, Pharmaceutical Press, 2009:129-133.
- [39] Dua S, Mahant S, Tiwari R. Influence of process and formulation variables on physical properties of the pellets using a 2<sup>3</sup> factorial design. *Int J Pharm Sci Rev Res* 2011; 7: 47-50.
- [40] Sinha VR, Agrawal MK, Kumria R. Influence of formulation and excipient variables on the pellet properties prepared by extrusion spheronization. *Curr Drug Deliv* 2005; 2: 1-8.
- [41] Clarke GM, Newton JM, Short MB. Comparative gastrointestinal transit of pellet systems of varying density. *Int J Pharm* 1995; 114:1-11.
- [42] Devereux JE, Newton JM, Short MB. The Influence of density on the gastrointestinal transit of pellets. *J Pharm Pharmacol*,1990; 42: 500-501.
- [43] Rowe RC, Sheskey PJ, Quinn ME. Lactose, monihydrate. In: *Handbook of Pharmaceutical Excipients*, Sixth editions, Pharmaceutical Press, 2009: 364-369.
- [44] Rojas J, Kumar V. Comparative evaluation of silicified microcrystalline cellulose II as a direct compression vehicle. *Int J Pharm* 2011; 416(1):120-8.

[45] Horisawa E, Danjo K, Sunada H. Influence of granulating method on physical and mechanical properties, compression behavior, and compactibility of lactose and microcrystalline cellulose granules. *Drug Dev Ind Pharm* 2000; 26(6):583-93.

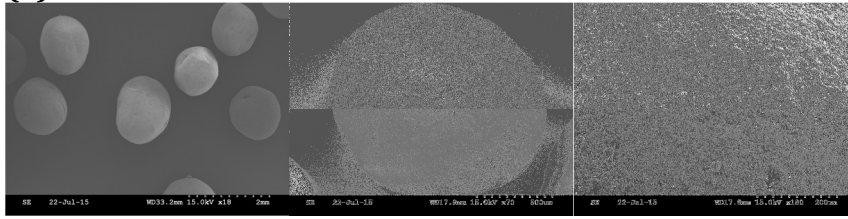
[46] Luukkonen P, Newton JM, Podczek F, Yliruusi J. Use of a capillary rheometer to evaluate the rheological properties of microcrystalline cellulose and silicified microcrystalline cellulose wet masses. *Int J Pharm* 2001; 216(1-2):147-57.

[47] Sousa JJ, Sousa A, Podczek F, Newton JM. Factors influencing the physical characteristics of pellets obtained by extrusion-spheronization. *Intl J Pharm* 2002; 232:91-106.

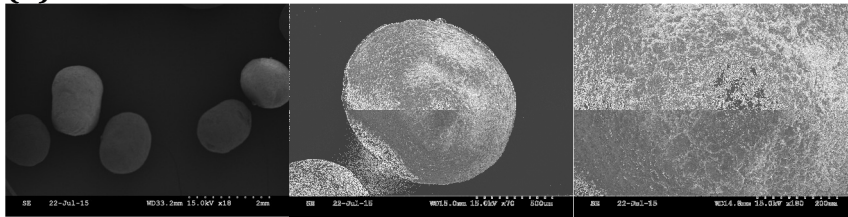
[48] Teixeira AZA. Compaction characteristics of the powder from the seed coat of *Tingui* (*Magonia pubescens*). *Estud. Biol* 2007;29(68/69):277-282.

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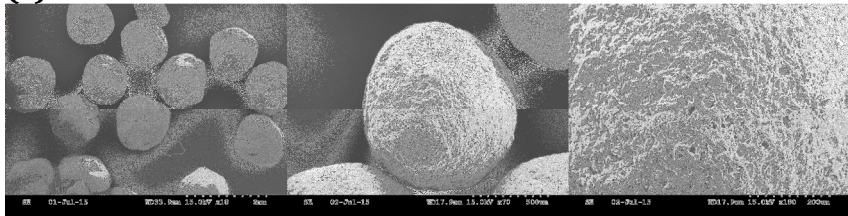
(a)



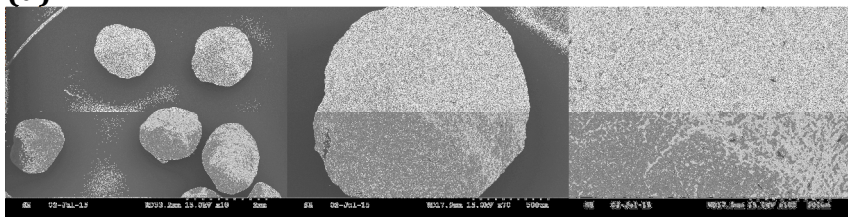
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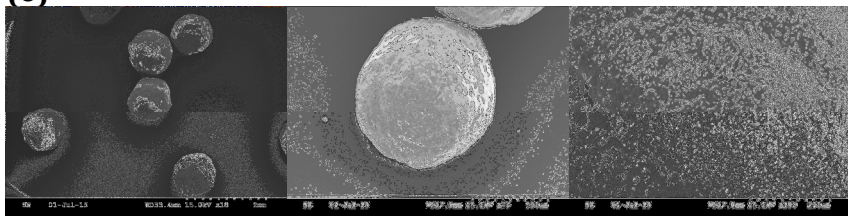
(c)



(d)



(e)



(f)

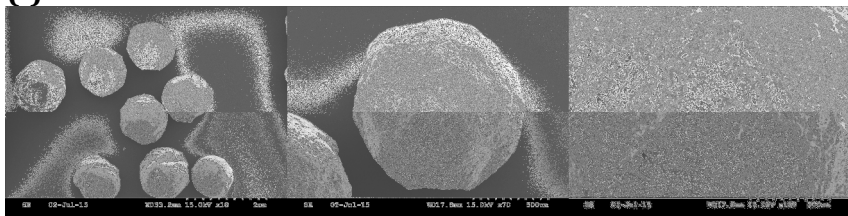


Figure 1 SEM images of typical pellets at different magnifications; (a) P2b; (b) A2; (c) P5, (d) A5, (e) P8 and (f) A8.

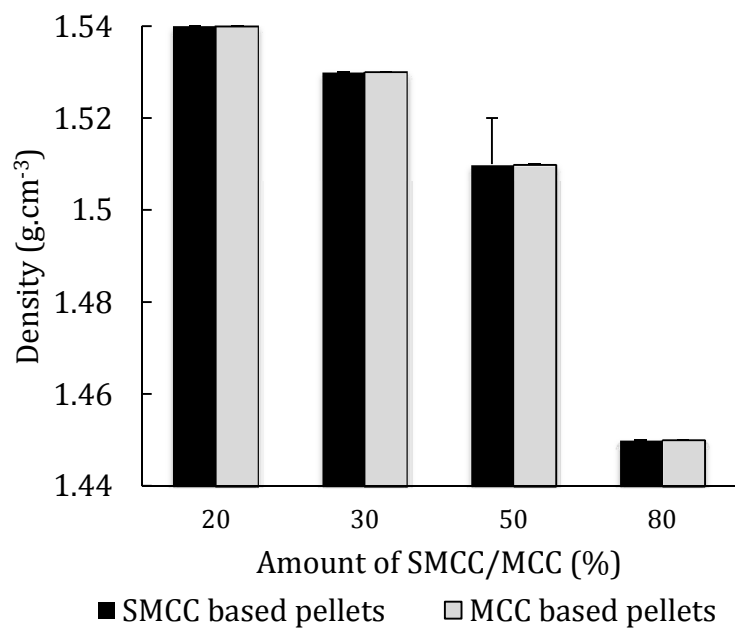


Figure 2 Pellet density as determined by helium pycnometer.

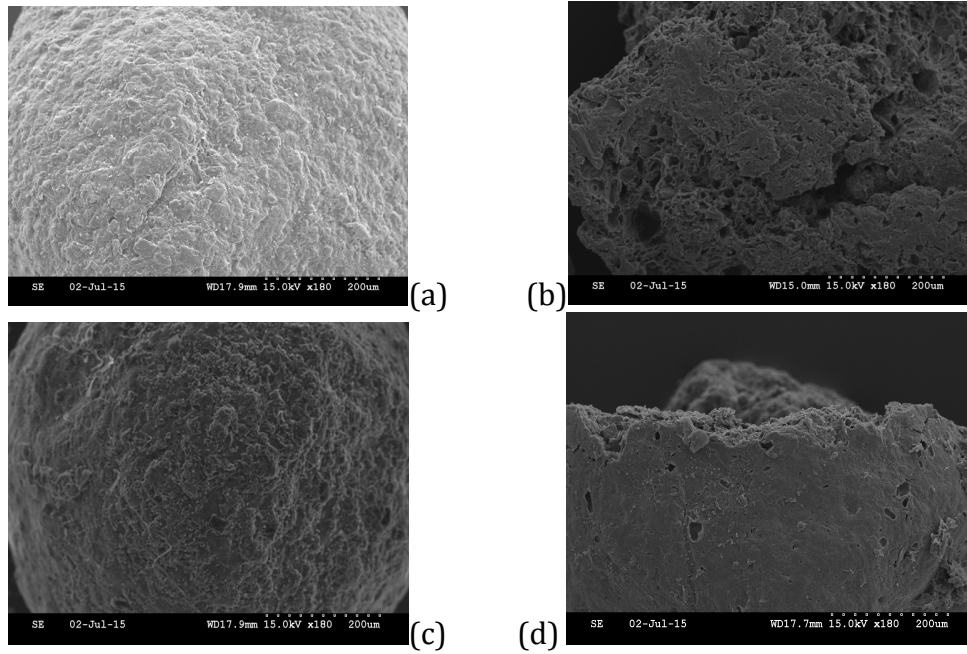


Figure 3 SEM images of P4a (40% SMCC) and P8 (80% SMCC) before (a & c respectively) and 45 minutes after (b & d respectively) disintegration test.

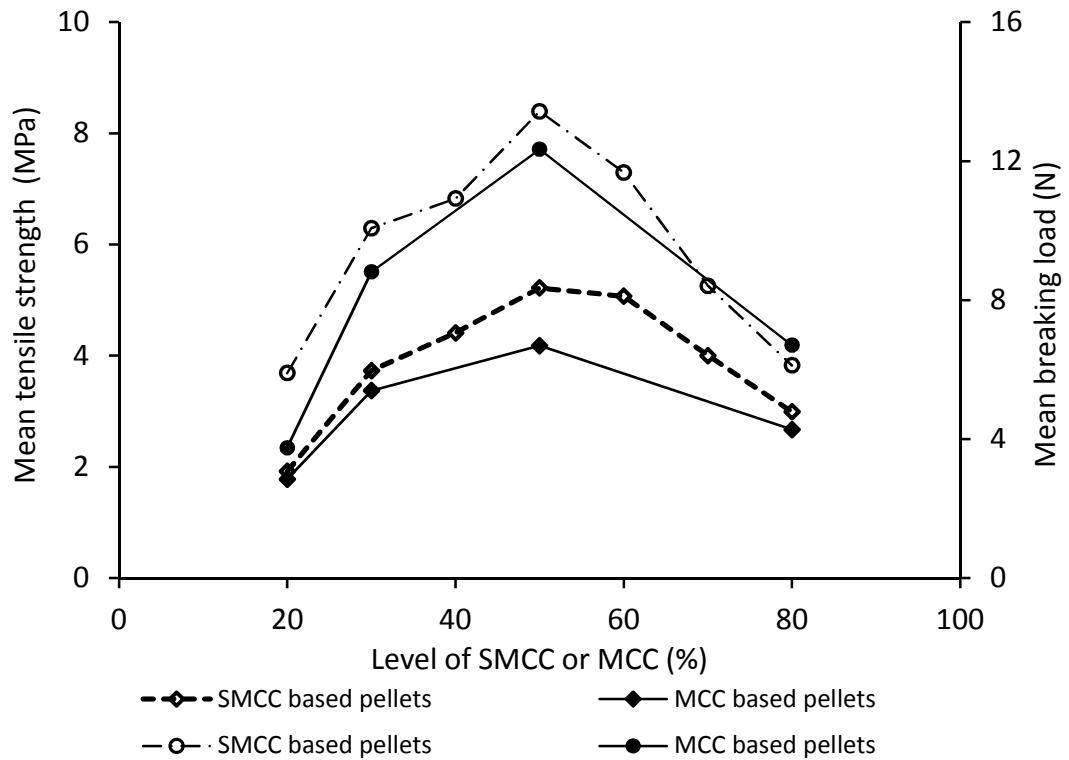


Figure 4 Mean breaking load and surface tensile strength of either SMCC or MCC based pellets. Symbols represent ( $\blacklozenge$ , closed diamond) surface tensile strength of MCC based pellets; ( $\diamond$ , open diamond) surface tensile strength of SMCC based pellets; ( $\bullet$ , closed circle) breaking load of MCC based pellets and ( $\circ$ , open circle) breaking load of SMCC based pellets.



Table 1 Ingredients, process parameters for production and characteristics of pellets. The values represent mean  $\pm$  standard deviation where applicable.

ID	SMCC/ MCC lactose*	SMCC/MCC : water**	Spherulizer speed (rpm)	Yield (%)	Fine fraction (%)	Coarse fraction (%)	Modal class (mm)	D <sub>50</sub> (mm)	K <sub>D</sub> R (mm)	Aspect ratio	Circularity	Density (g·cm <sup>-3</sup> )	Tensile Strength (MPa)	Breaking load (N)	Disintegration time (min)
P2a	2:8	1:1.6	1200	93.37	1.03	0.26	1-1.18	1.03	0.18	1.30 ±0.10	0.89 ±0.08	1.34 ±0.01	1.03	3.21 ±1.31	3.26 ±0.00
P2b†	2:8	1:1.6	1400	93.10	1.23	1.72	1-1.18	1.10	0.18	1.13 ±0.03	0.93 ±0.03	1.33 ±0.00	1.92	3.90 ±1.31	6.49 ±0.00
P2c	2:8	1:1.6	1600	84.15	1.34	11.63	1.18-1.4	1.23	0.23	1.12 ±0.04	0.91 ±0.07	1.34 ±0.00	1.81	3.76 ±1.21	6.49 ±0.00
P2d	2:8	1:1.6	2000	***	***	***	***	***	***	***	***	***	***	***	***
P2e	2:8	1:1.5	2750	***	***	***	***	***	***	***	***	***	***	***	***
P3	3:7	1:1.3	2750	93.30	0.00	0.26	1-1.18	1.01	0.24	1.10 ±0.04	0.94 ±0.02	1.34 ±0.00	3.73	10.07 ±1.31	343
P4a	4:6	1:1.3	2750	61.36	0.00	38.44	1.18-1.4	1.34	0.27	1.14 ±0.06	0.87 ±0.08	1.33 ±0.00	4.27	13.78 ±1.31	343
P4b	4:6	1:1.43	2750	24.73	0.07	4.70	1.4-1.7	1.50	0.13	1.17 ±0.07	0.92 ±0.03	**	4.33	15.34 ±2.32	***
P4c†	4:6	1:1.4	2750	91.93	0.24	0.82	1-1.18	1.13	0.22	1.11 ±0.06	0.91 ±0.04	1.33 ±0.00	4.41	10.92 ±1.31	343
P5	3:3	1:1.3	2750	84.89	0.07	3.19	1-1.18	1.18	0.30	1.10 ±0.03	0.93 ±0.02	1.49 ±0.01	3.22	13.43 ±2.83	343
P6a†	6:4	1:1.23	2750	97.80	0.00	1.42	1-1.18	1.04	0.22	1.11 ±0.04	0.89 ±0.08	1.48 ±0.00	3.07	11.67 ±3.31	343
P6b	6:4	1:1.2	2750	76.41	1.30	0.22	0.71-1	0.83	0.20	1.10 ±0.04	0.91 ±0.03	1.47 ±0.01	4.8	11.33 ±1.83	343
P6c	6:4	1:1.1	2750	84.88	0.23	0.70	0.71-1	0.83	0.18	1.10 ±0.03	0.93 ±0.03	1.47 ±0.01	3.27	12.38 ±1.61	343
P7	7:3	1:1.1	2750	93.49	0.43	0.00	1-1.18	1.00	0.24	1.11 ±0.03	0.89 ±0.06	1.46 ±0.01	4	8.41 ±1.0	343
P8	8:2	1:0.9	2750	86.47	3.08	0.00	0.71-1	0.91	0.26	1.10 ±0.03	0.93 ±0.02	1.42 ±0.00	2.99	6.12 ±0.87	343
A2	2:8	1:1.6	1400	92.33	0.13	0.10	1-1.18	1.04	0.26	1.21 ±0.09	0.94 ±0.08	1.34 ±0.00	1.47	3.73 ±0.72	3.33 ±0.00
A3	3:7	1:1.3	2750	94.42	0.00	0.00	0.71-1	1.00	0.23	1.11 ±0.06	0.94 ±0.04	1.33 ±0.00	3.27	8.81 ±1.76	343
A5	3:3	1:1.3	2750	80.93	0.16	3.03	1-1.18	1.13	0.23	1.13 ±0.07	0.93 ±0.02	1.31 ±0.00	4.2	12.34 ±2.88	343
A8	8:2	1:0.9	2750	77.37	1.84	1.86	0.71-1	0.97	0.30	1.09 ±0.03	0.93 ±0.01	1.43 ±0.00	3.1	6.70 ±0.36	343

\* SMCC/MCC: lactose denotes as either ratio of Prosolv<sup>®</sup> SMCC 50 or Avicel PH101 to lactose. \*\* SMCC/MCC: water denotes as either ratio of Prosolv<sup>®</sup> SMCC 50 or Avicel PH101 to water.

\*\*\* indicated tests were not performed due to low yield. For formulations where multiple batches were produced, \* represents the pellet batches with the best size distribution and shape, and they were used for further analysis in the discussion section. D<sub>50</sub> = median diameter, K<sub>D</sub>R = interquartile range.