Micro particle surface layering through dry coating: impact of moisture content and process parameters on the properties of orally disintegrating tablets

Hamad Alyami[1], Jasdip Koner[2], Eman Z. Dahmash[3], James Bowen[4], David Terry[5, 6] & Afzal R. Mohammed*

[1] Aston School of Pharmacy, Aston University, Birmingham, B4 7ET, United Kingdom, +44-7454-741483, alyamihs@aston.ac.uk

[2] Aston School of Pharmacy, Aston University, Birmingham, B4 7ET, United Kingdom, +44-7725-071192, konerjs@aston.ac.uk

[3] Aston School of Pharmacy, Aston University, Birmingham, B4 7ET, United Kingdom, +44-7554-802160, dahmashe@aston.ac.uk

[4] Department of Engineering and Innovation, Open University, Milton Keynes, MK7 6AA, United Kingdom, +44-7903497498, james.bowen@open.ac.uk

[5] Children Hospital, Birmingham, B4 6NH, United Kingdom, +44-121-333-9793, david.terry@bch.nhs.uk

[6] Aston School of Pharmacy, Aston University, Birmingham, B4 7ET, United Kingdom, +44-121-333-9786, d.terry@aston.ac.uk

***Corresponding author**: Aston School of Pharmacy, Aston University, Birmingham, B4 7ET, United Kingdom, +44-121-204-4183, a.u.r.mohammed@aston.ac.uk

Abstract:

Objectives The aim of this study was to investigate the influence of processing parameters in dry coating on particle and dosage form properties upon varying the surface adsorbed moisture of microcrystalline cellulose (MCC), a model filler/binder for orally disintegrating tablets (ODTs).

Methods The moisture content of MCC was optimized using the spray water method and analysed using thermogravimetric analysis. Micro/macro property assessment was determined using atomic force microscopy, nano indentation, scanning electron microscopy, tablet hardness and disintegration testing.

Key findings The results showed that MCC demonstrated its best flowability at a moisture content of 11.2%w/w when compared to control, comprising of 3.9%w/w moisture. The use of the composite powder coating process (without air) resulted in up to 80% increase in tablet hardness, when compared to the control. The study also demonstrated that surface adsorbed moisture can be displaced upon addition of excipients during dry processing circumventing the need for particle drying prior to tabletting.

Conclusions It was concluded that MCC with a moisture content of 11%w/w provides a good balance between powder flowability and favourable ODT characteristics.

Keywords

Composite; nanoindentaion; disintegration; flowability; hardness

Introduction

In recent years, paediatric drug development has come to the forefront of research due to the incentives offered by regulatory bodies in the US and within the EU, including financial rewards and patent extensions for drug formulations[1]. In the past, big Pharma companies were more focused on developing adult friendly dosage forms due to the high profit margins and perceived lower risk of development. Children are a unique entity in the fact that they develop at a vast rate, from the day of birth to becoming adults, with the first 18 years of their lives sub classified in to several groups: Premature new-borns (<38 weeks gestational age); Term new-borns (>38 weeks gestational age); Neonate (0-30 days); Infant (1month-2 years); Young Child (2-6 years); Child (6-12 years) and Adolescents (12-18 years)[2]. This presents various formulation challenges, primarily pharmacokinetic and pharmacodynamic, as absorption, distribution, metabolism and excretion are highly varied throughout these years, and the dose for administration needs to be tailored throughout the paediatric age range[3].

For paediatric dosage forms to be acceptable there are a number of practical aspects that also need to be considered such as, risk of choking for solid dosage forms, elegance, palatability and acceptance of the dosage form by the child[4]. Historically oral liquid dosage forms, such as syrups, have been the dosage form of choice for many paediatric patients due to their ease of administration and dose flexibility. Nonetheless, oral liquid dosage forms have many disadvantages such as: poor taste of bitter drugs; drug stability, with many antibiotic formulations having 7-14 day expiry after reconstitution; storage conditions, with many being items that need to be kept in the fridge and transportability issues, with liquid bottles occupying large space. Consequently, the WHO recently stated that young children may be treated with oral solid dosage forms, such as orally disintegrating tablets (ODTs) and as such there is a concerted effort in understanding and developing technologies to formulate these dosage forms [5].

ODTs are a dosage form designed to disperse on the tongue when it comes in to contact with saliva, thereby reducing the need for tablets to be swallowed whole without water, making them ideal dosage forms for paediatric populations. The standards for a dosage form to be classed as an ODT is that 'it must disintegrate rapidly in the oral cavity, with an in-vitro disintegration time of approximately 30 seconds or less', and in general have a weight of no more than 500mg[6]. ODTs combine the advantages of solid and liquid dosage forms with some novel ODT technologies allowing high drug loading whilst offering pleasant mouth feel with an acceptable taste.

Although ODTs present many advantages over other paediatric formulations, there are several challenges associated with these types of tablets. There are two common methods of manufacture; freeze drying, that produces rapidly disintegrating tablets which are often mechanically weak and require specialised packaging and equipment, and direct compression[7]. Direct compression utilises traditional tableting equipment and requires no specialised processing techniques to form robust and fast disintegrating ODTs. Due to the simplicity of the method, excipient and bulk powder characteristics need to be considered. Flowability of the bulk powder is of particular importance as the powder needs to be able to flow in to the dies at a consistent rate to form uniform tablets that have a consistent weight and drug content. As the tablets disintegrate within the oral cavity, taste is a key factor that needs to be evaluated, as poor palatability of the dosage form would lead to poor medication adherence. This can often be solved using flavourings and sweeteners, with more complex systems such as film coating of granules and microencapsulation also used, which can often increase development costs and also expose active pharmaceutical ingredients (APIs) to unfavourable conditions. One of the simplest ways to address this issue is the use of mannitol, a polyol isomer of sorbitol, which has a very sweet taste and cooling effect in the mouth and can often provide a palatable dosage form [8]. It has dual functionality in that it is also a popular binder/filler used in ODTs due to its advantages in producing acceptable dosage forms. Other considerations specifically for ODTs include disintegration time, as this needs to be optimised

to allow the dosage form to disintegrate within specified timeframes. This can often involve the use of superdisintegrants in the powder blend, such as crospovidone, which uses capillary action to induce water uptake in to the tablet through wicking mechanisms, resulting in a rapid volume expansion of the tablet and subsequent break-up of the tablet structure[9]. Inclusion of superdisintegrants in to ODTs can increase moisture sensitivity in ODTs. High levels of moisture in the final dosage form can present difficulties particularly in ODTs, due to their ability to uptake moisture from the surroundings as well as their fast disintegrating properties[10] Including mannitol can often aid in reducing the hygroscopic nature of the ODT, due to its non-hygroscopic nature[8]. Alongside this, powder deformation processes need to be evaluated to minimise the elastic deformation properties of the powder, which could lead to capping and lamination of the tablet [11]. MCC is a common excipient employed in ODTs as it has very high compactability due to its plastic behaviour, leading to robust dosage form manufacture[12].

The objective of this study was to study the effects of moisture content on MCC, which is a model filler/binder for ODTs, in order to optimise the moisture levels to produce the most advantageous powder/tablets. A novel composite coater developed in our laboratory was used to investigate the effect of process parameters on the moisture content, as well as studying the effect of excipient addition on the resultant moisture. It was hypothesised that the powder coater could be used as a novel tool to optimise moisture levels within MCC to a desirable quantity, producing not only a favourable pre-processed material with good flowability and compaction properties, but also a suitable tableting excipient to formulate robust ODTs without a resultant compromise in disintegration time.

Materials and Methods

Materials

D-mannitol, magnesium stearate and sodium chloride salt (NaCl) were purchased from Sigma-Aldrich (Pool, UK), while microcrystalline cellulose (MCC) (Avicel PH-200) was

obtained from FMC BioPolymer Europe (Brussels, Belgium). Crospovidone (CrosPVP, Polyplasdone® XL-10) was obtained from Ashland (Wilmington, USA). All the ingredients were of pharmaceutical grade.

Methods

Optimisation of Moisture Content

The first step of the moisture process began with weighing a precise amount of the original MCC powder (20g) (MCC1) which was spread evenly on a tray. In the next step, increments of distilled water were added at approximately 30 second intervals without any shaking. The moisture content was tested at intermittent durations until the desired moisture contents 11.2% (MCC 2) and 40% (MCC 3) were obtained. The amount of added water was approximately 5-10 ml providing moisture content between 10% and 40% for the MCC powder. The moist powders were transferred into a small airtight container and sealed using para film.

Sieving process, interactive and composite powder coating technique

The two key excipients studied included microcrystalline cellulose (MCC) and mannitol. Selected particle sizes of both D-mannitol and MCC were obtained by sieving. MCC was passed through sieve with mesh size of 355µm and the sample retained at sieves with pores size of 250µm was used. D-mannitol was sieved using 38µm sieve and particles retained on the 20µm sieve were used. The composite mixing process was carried out considering several critical operating parameters; speed of the mixer, mixing time and the use of air flow. As for the materials used, the parameters considered were pertinent to the guest loading percentage, measured in weight per weight, and the type of carrier material in terms of particle size and shape. Samples were tested alongside interactive mixtures with the same content, but mixed at low speeds (300rpm) and a shorter time (10 minutes). The formulation and the processing parameters are listed in **Table 1** below.

Characterising interactive and powder coating

Measurement of powder moisture content using TGA

A thermogravimetric analyzer, Pyris 1 TGA from Perkin Elmer (Massachusetts, USA) was used to measure the moisture content of all powders. 2-5 mg of each sample was loaded onto the TGA pan and heated between 30-300°C at a scanning rate of 30°C/min and held for 5 minutes at 100°C under a nitrogen stream. Pyris Manager Software (version 5.00.02) was used for analysing the obtained thermograms. Moisture content was obtained by calculating Δy for each run between 70°C and 130°C. All samples were analyzed in triplicate.

Assessment of powder flow properties by measurement of angle of repose

The angle of repose measurement was performed using the recommended British Pharmacopeia procedure[13]. Approximately 10 g of powder was poured through a funnel into a base free from vibration to form a pile. The funnel was positioned 2 - 5 cm from the top of the powder pile as it was forming. Angle of repose was determined by measuring the height of the pile (h) and diameter of the base (d); then angle of repose (α) was calculated from the equation:

$$tan\alpha = h \div (0.5 \times d)$$

Scanning electron microscopy (SEM)

The morphology of MCC at different moisture contents, D-mannitol, the mixture and the coated powder particles were examined using a Stereoscan 90 from Cambridge Instruments (Crawley, UK) scanning electron microscope (SEM). Approximately 1-2 mg of each material was placed onto a double-sided adhesive strip on an aluminium stub. The specimen stub was coated with a thin layer of gold using a Polaron SC500 sputter coater from Polaron Equipment ltd. (Watford, UK) at 20 mA for 3 min followed by sample examination using SEM. The acceleration voltage (kV) and the magnification can be seen on each micrograph. Various magnifications were applied to identify characteristics of the powders.

159 **Particle size analysis**

160 Particle size of the powders was measured by the laser diffraction technique using HELOS/BR
161 particles size analyzer equipped with a RODOS dry disperser with VIBRI/L vibrating feeder,
162 from Sympatec (Clausthal-Zellerfeld, Germany). The measuring range of the lens was 0 -
163 175µm. About 1 g of each powder was placed in the feeder tray and the run started at trigger
164 condition of 2% Copt (optical concentration) for 10 sec with a powder dispensing pressure of
165 2bar. Volume mean diameter (VMD) was recorded for the powders and all the measurements
166 were examined in triplicate.

167 **Atomic Force Microscopy (AFM)**

168 Acquisition of topographical data was performed using a NanoWizard II AFM (JPK, UK)
169 operating in force scan mapping mode under ambient conditions (18^{o}C, 50% relative
170 humidity). This involved the use of a scanner with a maximum lateral range of 100 × 100µm
171 and a maximum vertical range of 15µm. Data acquisition was performed using rectangular Si
172 cantilevers (HQ:CSC17/noAl, MikroMasch, Estonia) having pyramidal tips with 10nm nominal
173 radii of curvature. Cantilever spring constants were on the order 0.3N/m, calibrated according
174 to the method reported by [14]. Topography was assessed over a 2µm x 2µm area using a grid
175 of 128 x 128 pixels. Data was acquired by driving the fixed end of the cantilever at a velocity
176 of 50µm/s towards the sample surface, whilst monitoring the deflection of the free end of the
177 cantilever using a laser beam. Upon making contact with a surface feature, the height of the
178 contact point was recorded, representing one pixel in the image, which was converted into a
179 map of surface topography. A maximum compressive load of 10nN was applied to the surface
180 during data acquisition.

181 **Nanoindentation**

182 The hardness and Young's modulus of the powder wafers was measured using a
183 Nanoindenter XP (MTS, USA) employing a diamond-coated Berkovich indenter. 36
184 indentations were performed perpendicular to the wafer surface, each in a different

unperturbed area. Samples were indented at a strain rate of $0.05s^{-1}$ to a maximum depth of 500nm. The hardness and Young's modulus were calculated from analysis of the load-displacement data, fitting a second order polynomial to the unloading curve (**Figure 1**) [15]. The Poisson's ratio of the powder was assumed to be 0.3. In this approach the total penetration depth is assumed by the sum of the plastic depth (contact depth), δ_c, and the elastic depth, δ_e, which represents the elastic flexure of the surface during loading. Thus the total penetration depth, δ, is given by

$$\delta = \delta_c + \delta_e$$

and

$$\delta_e = \varepsilon\,(P \div Su)$$

Where S_u is the slope of the unloading curve at maximum load (see fig 3), P is the indenter load and ε is a constant which depends on indenter geometry. So the hardness, H, is then given by equation

$$H = P \div A_c$$

Where A_c is an ideal Berkovich indenter constant .Young's modulus can be determined from the slope of the unloading curve using a modified form of Sneddon's flat punch equation where

$$S_u = \gamma\beta \frac{2}{\sqrt{\pi}} Er\sqrt{\mathrm{Ac}}$$

Where γ is the correction factor, β is the cone to pyramid indenter conversion factor and Er is the contact modulus which can be derived from Young's modulus € and Poisson's ratio (v) of the indenter and the test material via

$$\frac{1}{Er} = \frac{1 - vm^2}{Em} + \frac{1 - vi^2}{Ei}$$

Where the m and i refer to the test material and indenter, respectively

Calculation of surface coverage

Surface coverage was calculated using the equation and method described in[16]. The amount of guest material in weight percentage (Gwt%) required to achieve 100% coverage within the given parameters was as follows:

$$Gwt\% = \frac{Nd^3\ pd}{(D^3\ pD) + (Nd^3\ pd)} \times 100$$

Where N is:

$$N = \frac{4(D+d)^2}{d^2}$$

Where d is the diameter of guest particle, D is the diameter of the host particle, pd is the density of the guest particle and pD is the density of the host particle.

Tablet Preparation and Characterization

Ternary mixture tablets were prepared comprising of the excipients at fixed quantities: 30% w/w of MCC, 5% w/w crospovidone, and 64.5% w/w mannitol and 0.5 % w/w magnesium stearate (lubricant). Powders were processed as interactive/composite mixes and compacted into 500 mg tablets under compression force of 10 KN, with a dwell time of 6s before compression force was released. The tablet press utilized for preparing the tablets was a bench-top semi-automatic hydraulic press from Specac Ltd. (Slough, UK) equipped with flat faced dies of 13 mm diameter. Tablets were characterized for porosity, hardness, disintegration time and friability. All tests were carried out in triplicate (n=3).

Tablet hardness

A tablet hardness tester from Schleuniger (Thun, Switzerland) was used to examine the hardness of three tablets of each formulation. Hardness is the force required to break up the

tablet from its original structure and was measured in Newtons (N) for this study. All measurements were carried out in triplicate and the values reported as mean ± standard deviation.

Tablet disintegration

The disintegration time was obtained using the standard USP moving basket apparatus (USP Convention, 2005). A ZT3 disintegration tester from Erweka (Heusenstamm, Germany) was used. A tablet was placed in the disintegration basket (without using a disk) which was raised and lowered at a constant frequency of 30 cycles/min in the disintegration medium. Distilled water (800 mL) maintained at 37°C was used as the disintegration medium while disintegration time was recorded for one tablet at a time to improve accuracy of recording. Time of disintegration was recorded when all the disintegrated fractions of tablet passed through the mesh at the base of the disintegration basket.

Tablet friability

The ability of the tablets to withstand mechanical stress, known as friability was measured using a Roche friabilator from J. Engelsmann AG (Ludwigshafen, Germany). 10 tablets were rotated at 25 rpm for 100 revolutions. Tablets were de-dusted before and after the test, and friability expressed as the percentage loss in weight. The percentages loss in weight (% Friability) was calculated using the following equation.

$$\%\, Friability = \frac{Initial\, Weight - Final\, weight}{Initial\, weight} \times 100$$

Tablet porosity

Tablet porosity was measured using a helium multipycnometer from Quantachrome Instruments (Syosset, USA). One tablet was placed in a micro sample cell of the instrument and the true volume V_t was obtained using the equation:

$$V_t = V_C - V_R \left(\frac{P1}{P2 - 1}\right)$$

Where V_t is true volume of the sample, V_C is volume of the sample cell, V_R is the known reference volume, P1 is atmospheric pressure and P2 is pressure change during determination. V_t was used to calculate the true density of the tablet by weighing the tablet and substituting the values into:

$$True\ Density = \frac{Tablet\ Weight}{True\ Volume}$$

Porosity (ε) was calculated using the equation:

$$\varepsilon = 1 - \left(\frac{Bulk\ Density}{True\ Density}\right)$$

Bulk density was calculated from:

$$Bulk\ Density = \frac{Tablet\ Weight}{Bulk\ Volume}$$

Bulk volume was acquired by measuring the radius (r) and thickness (h) of the tablet using a digital calliper and substituting in the equation for volume of a flat-faced tablet:

$$V = \pi \times r^2 \times h$$

Statistical analysis

One way ANOVA followed by Tukey post-hoc test or student t-test were performed according to the obtained results, using GraphPad Prism 6.02 software (California, USA). Statistical significance was considered at a p value <0.05. Where applicable, all results are presented as mean ± SD for triplicate measurements to account for the noise encountered within the experiments.

Results and Discussion

The work presented in this study provides a systematic investigation on the impact of moisture content of MCC on powder and tablet performance. Moisture content of the pre and post processed materials; MCC, D-mannitol, crospovidone, magnesium stearate and the ternary mixtures were analysed using TGA for loss on drying. These excipients were selected based on their role as binders, fillers, disintegrants or dual functional binder/disintegrant systems within ODTs. The majority of the work on moisture content was conducted with MCC as it is a hygroscopic excipient that is commonly employed within ODTs as a binder/filler[17].

Moisture content of the investigated excipients

Figure 2 (a) shows the levels of moisture obtained from each of the studied excipients through TGA analysis. It was seen that D-mannitol had the lowest moisture content, at about 0.5% w/w compared to MCC, which had a moisture content of 3.8% w/w. This was in line with the literature findings where the moisture content of MCC was reported to be around 3-4% w/w[18]. with D-mannitol expected to have low moisture content due to its non-hygroscopic nature[8].

In this study it was hypothesised that the levels of moisture within MCC influenced the physio-mechanical properties of the particles, including their hardness/tensile strength, flow and their compaction behaviour. In order to achieve different levels of moisture within MCC, the micro-spray method was used to increase levels of adsorbed water in the MCC to two different levels compared to the control MCC (4%) (MCC 1), which had not been subjected to moisture addition. The moisture contents investigated were 11% w/w (MCC 2) and 40% w/w (MCC 3). The three MCC powders were then subjected to a range of investigations to ascertain the effect that the moisture had during processing, addition of further excipients and on the tablet properties of the ODTs.

Effect of moisture content on morphology and flow of MCC

Good flow properties are a requirement for the successful manufacturing of tablets as it affects mixing, content uniformity, tablet compression and scale-up operations[19]. Flow properties of the materials tested were primarily affected by the size and shape of the particles within the powder, which in turn affected the cohesivity and the mechanical interlocking between the particles[20]. Flow properties were evaluated before mixing/tableting was carried out for the different MCC powders. Powder flow properties of the different MCC powders were assessed by measuring the angle of repose. The results showed significant differences (ANOVA, $p<0.05$) between the angle of repose of the powders, with MCC 2, at 11%w/w moisture content, demonstrating the best flowability with a low angle of repose at 29.60±0.86°, as shown in **Figure 2**(b) when compared to the control MCC, which had a fair flow, with the angle of repose of 38.52±0.67°. However at high moisture content of 40%w/w (MCC 3), poor flow was observed, with the angle of repose at 52±0.61°, indicating that high levels of moisture significantly worsened the flow properties of the powder[21],

At low moisture levels, water on the particle surface acted as a lubricant by decreasing friction and increasing the flowability of the powder thereby allowing the particles to move more easily over each other. For MCC2 it can be hypothesised that the moisture was able to act as a lubricant and increased the distance between the particles which also had the dual effect of reducing the effect of the van der Waals forces and reducing the cohesive forces. Once monolayer coverage was achieved, additional water did not significantly contribute to the lubricating and spacing effect and therefore further enhancements in flowability were minimal[22],

On the other hand, MCC showed a sharp decrease in flowability with increasing moisture content up to 40% W/W. This was attributed to the increased cohesion from the stronger liquid bridges formed from the condensed water on the surface of the particles. At higher moisture levels, the water possibly increased cohesion through stronger liquid bridges thereby reducing

flowability. Furthermore, water could primarily affect cohesion by increasing capillary forces through strengthening liquid bridges between the particles[23, 24]. When the angle of repose test was carried out, it was also observed that MCC adhered to the funnel, (**Figure 2**(e)), demonstrating that not only did the powder become more cohesive in nature, it also became more adhesive to external surfaces, indicating a worsening flow.

Analysis of SEM images after curing of MCC powder showed a slight enlargement in size with MCC 2 (at 11% moisture content), as shown in **Figure 2** (g) which possibly was an additional factor for improved flowbaility, as the larger particle size results in a reduction in cohesivity of the particles due to lower electrostatic forces, thereby enhancing the flow of particles [25]. It could also be said that the fine particles contained within the powder were also able to agglomerate/coat the larger particles, resulting in an increased particle size, due to the increased cohesivity, which reduced the overall cohesiveness of the blend and synergistically worked with the lubricating effect of the surface adsorbed water to improve the flow of MCC.

The effect of process parameters on MCC moisture content

To assess the effects of processing parameters on the moisture content of the MCC powders, three different parameters were used with each of the powders of MCC to analyse the effect on the resultant moisture content.

In this study a novel composite coater designed and built in our laboratory was used as the mixer of choice, and the effect of processing parameters within this device were assessed **(Table 1)**. The first parameter was to mix the powder at a low speed of 300rpm for 10 minutes to achieve interactive mixture (10 minutes was chosen as previous work in the group had shown that this duration produced a homogenous interactive mix). The second processing parameter included the composite coater at a speed of 1500rpm for 60 minutes, which would be used to form composite dry coated particles due to the high shear forces generated by the

device. The third parameter had the device at the same speed and time as the second parameter (1500rpm for 60 minutes) but with the inclusion of air to increase the deagglomerating and shear forces during mixing and to aid and increase the dry coating capabilities of the excipients used in the mix. The resultant moisture content of the three MCC powders after undergoing the different processing parameters are displayed in **Table 2**.

The interactively mixed powders at 300rpm are shown in **Figure 3**(b). The results showed no significant difference (ANOVA $p>0.05$) between the moisture content over time, indicating the mixing method had little effect on the moisture. Similarly, **Figure 3** (b) shows that no significant difference in moisture content was observed using composite mixing without including air pressure (ANOVA $p>0.05$) in all three powders.

Results of the moisture content over time using air in the mixing process are shown in **Figure 3** (c) and demonstrated that the use of air at a mixing speed of 1500 rpm resulted in a significant decrease in the moisture content of MCC ($p<0.05$). This could possibly be attributed to the formation of vortexes/whirlpools within the system upon fluidisation of powder bed, which was demonstrated by computational fluid dynamics (CFD) (data not shown). This vortex was responsible for the fluid environment in the chamber resulting in the enhancement of the drying of the powder; hence there was a large reduction in moisture content of the powders when air was introduced during mixing. This led to the hypothesis that use of air in the processing of high moisture excipients could therefore be used to optimise levels of moisture within the excipient to the user's desired levels, with processing times altered according to the required final moisture content.

Mechanistic investigation of adding excipients and its effect on the moisture content of MCC

To assess the effects of excipient addition on moisture content, mannitol and crospovidone were added to the different MCC powders. For interactive mixing, all three materials were added together and mixed for 10 minutes. For composite coating, excipients were added in a two-step process. Firstly to optimise the amount of mannitol added to form a full surface coverage around the MCC particles, surface coverage was calculated using equations by Yang et al (2005) with the following parameters; true density of MCC being 1.94g/cm$_3$ and D-mannitol 1.67 g/cm3; particle size of MCC being 2 50µm and D-mannitol 25.9µm, resulting in the percentage per weight of mannitol to achieve complete coverage calculated at 30.28%. This amount of guest particle (mannitol) was in agreement with the results stated in [16] as with a volume ratio of 5 the average coverage was around 56%. The value for surface coverage would be significantly reduced upon the reduction in particle size of mannitol or increase in particle size of MCC. The second step involved the addition of the remaining portion of the mannitol, alongside the addition of the crospovidone which was mixed for a further 30 minutes to form the final mixture.

Figure 4(a-c) show the moisture content profiles of the interactive against compositely mixed powders. All graphs indicated a reduction in the moisture content when the materials, in particular mannitol, were added to MCC, compared to MCC alone (ANOVA, $p<0.05$). With the interactive mix there was a large drop in the MCC moisture content for all three of the powders tested when the excipients were added to the powder blend and mixed over the 10 minute time period. In terms of the composite blends, SEM images, in **Figure 4**(e&f), showed that the mannitol was attached to the surface of MCC 2 particles and formed a coat around the MCC. **Figure 4**(b&c) showed the moisture loss of the two composite coating processes, without air and with air respectively, and both indicated very large drops in moisture content after 60 minutes, due to the addition of the excipients. With the mixing that included air, as shown in

Figure 4(c), the moisture content was expected to reduce more dramatically as the air within the chamber aided in the drying of the MCC powder. Alongside the use of air, the addition of excipient resulted in around 35% of moisture being lost in the first 10 minutes for MCC 3. In comparison to the use of air alone **Figure 3**(c) where the moisture loss after 10 minutes was around 25%, it showed that the addition of excipients was a key factor in the loss of moisture from the MCC particles. Comparing air and excipients, it was seen that the moisture loss of the MCC at 1500 rpm with air was very similar to when the mannitol was added to the MCC without air at a 1500 rpm mixing speed, with the moisture content of MCC 3 dropping to around 15% in both cases.

It was hypothesised that the water particles acted as a guest molecule and surrounded MCC during the introduction of external moisture. However, once the mannitol was added to the mix, it attaches itself to the surface of the MCC during the coating process, to replace water molecules, as there was a difference in the densities between mannitol and water, with water having a relative density of 1g/cm^3 and mannitol density being 1.67g/cm^3. Therefore, it was assumed that water droplets were knocked out from the surface of MCC by mannitol, which resulted in the reduction in the moisture content observed in **Figure 4**(d). Of particular interest was the composite mix without air, shown in **Figure 4**(b), where there was a large loss of moisture observed upon the addition of the first portion of mannitol, with around 25% moisture loss within 10 minutes of mixing followed by a plateau of moisture loss up until 30 minutes. However upon the second stage of excipient addition at 30 minutes, there was a further large drop in moisture content between 30-40 minutes by around 10%, which again plateaued. This indicated that the addition of other solid materials in to the powder blend clearly resulted in a loss in moisture as increased amounts of water were displaced from the surface of the MCC particles during the addition of further solid material. This supported the theory that water was substituted on the surface of MCC particles, as shown in **Figure** 4(d), as the addition of the excipients in two stages resulted in further loss of water at each stage of excipient addition.

To further understand these differences and to substantiate the above hypothesis, micro and macro properties of the materials were studied using a range of different techniques.

Investigation of the Micro and Macro properties of Ternary mixed powder blends

Micro Property assessment using AFM, Nano indentation and SEM

Nanonindentation was used to assess the micro-mechanical properties of the different MCC particles, with penetration resistance and hardness being two key features assessed. Wafers were prepared to give a uniform flat surface, as nanoindentation only tested local to the sample surface on to which the indents were performed. Wafers with the three different moisture contents of MCC and the interactive/compositely mixed powders were prepared and were subjected to the nanoindentation test, to examine viscoelastic behaviour and their elastic modulus and hardness. Modulus and hardness of the wafers prepared from the three MCC moisture contents and powders compositely mixed at 1500 rpm with and without air were obtained and displayed in **Figure 5**(a,b&c) respectively. With regards to the pre-processing materials, MCC 1, MCC 2 and MCC 3 pellets were subjected to the nanoindentaion test and the load penetration graph is shown in **Figure 5**(d). The penetration of the nanoindenter on the surface of the pellet was governed by many features, for example the degree of compaction of the particles in the pellet and the structure and porosity of the particles[26]. MCC 1 and MCC 2 showed similar profiles, indicating approximately the same absorption of energy during the loading/unloading cycle. In MCC 3 penetration was much less and the deformation predominantly showed an elastic profile. MCC 3 was found to have the lowest modulus at around 3.34 GPa and hardness around 17 Vickers, which could have been due to high moisture content and wide particle size distribution, giving rise to porous aggregates, which were subsequently confirmed by visual and SEM analysis in (shown in section 3.1). The

463 results of the modulus and hardness of the different MCC powders showed a significant
464 difference (ANOVA,$p<0.05$).
465
466 Data from AFM also showed that MCC 3 was composed primarily of smooth surface
467 topography particles with the lowest average roughness Ra of approximately 35nm, as shown
468 in **Figure 6**(a). This was possibly due to the high levels of adsorbed moisture on the surface
469 on the particles, which resulted in a smoother surface [27]. The highest modulus and hardness
470 was observed with MCC 2, and these values correlate to the AFM readings whereby particle
471 roughness was highest.
472
473 A major change in hardness and modulus was observed in compositely mixed blends shown
474 in **Figure 5**(b&c) compared to pre-processing materials. This experiment provided evidence
475 that MCC was coated by mannitol as a sharp decrease in hardness and modulus of the
476 particles was observed. The decrease in mechanical properties indicated that the surface of
477 MCC was coated with mannitol. Mannitol has lower compactability when used in tablet
478 formulation, giving tablets of a lower mechanical strength; hence, mannitol had undergone
479 fragmentation under pressure, resulting in the formation of weak wafers[28].
480 In addition, previous research from our group has stated that the needle shape of the particles
481 of mannitol results in its low compactability[20]. To further support the fragmentation pattern,
482 AFM topographical analysis was performed which showed a considerable number of
483 asperities that were liable to damage when slight force was applied using the AFM cantilever.
484 Additionally, morphological studies using SEM showed columnar/longitudinal particles for pure
485 mannitol in comparison to MCC which was primarily composed of irregularry shaped particles
486 with microfibrilar structure[20]. Using one way ANOVA, results of modulus and hardness
487 demonstrated no significance difference between composite mix with/without air flow ($p>0.05$).
488 Furthermore, AFM confirmed the smooth surface of particles when no air was included (**Figure**
489 **6**(e)), whereas, the composite mixing with air presented a very high roughness (Ra was 534
490 approaching approximately five times that of composite mixing without air) (**Figure 6** (a)).

Macro properties of ternary mixed powder blends

In this section tablet properties of the different ternary mixtures of powders containing the different MCC moisture content powders were investigated. Disintegration time, hardness and porosity were both affected by the increase in moisture content possibly as a result of the different densification mechanisms of the powder bed and particulate deformation due to the fragmentation of mannitol and plastic deformation of MCC[29].

Investigation of the effect of moisture content on mechanical properties of ODTs

The results of tablets made from ternary mixtures comprising of 64.5% w/w mannitol, 30% w/w MCC (different moisture contents), 5% w/w crospovidone and 0.5% w/w magnesium stearate showing the relationship between moisture content and hardness/friability, are depicted in **Figure 7**(a-c). With regards to the interactive mixture, using MCC 2 where the final moisture content of the powder came to approximately 2.7% w/w, provided tablets with increased compact strength whereas at higher moisture contents, using MCC 3 (>4% w/w final moisture content) a dramatic reduction in tablets hardness was obtained as shown in **Figure 7** (a&b). The initial increase in crushing strength of tablet compacts with increasing moisture content up to 2.7% w/w was possibly due to the hydrodynamic lubrication effect of moisture, which allowed a greater fraction of the applied force to be diffused through the compact on to the lower punch. Meanwhile, an initial increase in moisture content resulted in a higher crushing strength, due to increased particle-particle interaction. Consequently the increased moisture possibly improved plastic deformation[30].

With regards to the composite blend without the inclusion of air, it was clear that increased moisture content up to 2% w/w resulted in an improvement of the tablet hardness. For example, the MCC 2 formulation (2.1% w/w moisture content) had a hardness of 52N, whereas the hardness of tablets with MCC 1 (1.8% w/w moisture content) was 29N. It is possible that the increased amount of moisture contributed to an increase in the initial consolidation rate as

518 well as the final granule consolidation during compaction as the moisture acted as a low
519 viscous binder[31].
520
521 The use of the composite dry powder coating process without air to form a final 2.1% w/w
522 moisture content (MCC 2) resulted in enhancement of the hardness profile of the tablets, up
523 to 80%, when compared to 1.8% w/w moisture content powder (using MCC 1), as shown in
524 **Figure 7** (b). This was attributed to the strong adherence of the fine mannitol particles to the
525 surface of MCC. Furthermore, the increase in hardness due to the moisture content and
526 coating may have been due to the formation of a mono molecular layer of moisture around the
527 powder particles. This film of moisture could enable the formation of interparticle hydrogen
528 bonding and/or increased the van der Waals' forces, therefore smoothing out the surface micro
529 irregularities and dropping interparticle separation[32].
530
531 The presence of excessive moisture decreased the compact strength, by reducing the
532 hydrodynamic resistance and therefore increasing elastic recovery after ejection[33]. A high
533 compaction force and high moisture content may have also led to a significant moisture
534 squeeze out onto the particle surface, thus reducing interparticle bonding and thereby
535 increasing elastic recovery resulting in a reduction of the crushing strength[30]. A previous study
536 found that sodium chloride compacts containing higher moisture content had lower strength[18].
537 Another possible explanation for a decrease in hardness at high moisture content was the
538 formation of multilayers of water at the particle surface. These layers may have disturbed or
539 decreased inter molecular attraction forces and thus reduced tablet strength[34].
540
541 Overall, a proportional relationship between the tablet hardness and friability was seen; as
542 hardness increased the friability was improved in all approaches. For example, hardness in
543 **Figure 7**(a) showed that at 7.7% w/w moisture content, the tablets had the lowest hardness
544 value at 13.57±3.32N and the highest friability percentage at 7.6%. While, the highest

hardness of 51.9±2.35N with lowest friability of 2.38%, was found with 2.1% w/w moisture content as shown in **Figure 7** (b).

It was also observed that post friability test, capping of prepared tablets increased with the increased moisture content (>4% using MCC 3) as shown in **Figure 7** (g). The tendency to cap may have increased due to the weakening of the interparticle bonds as a result of the disruption of molecular forces and greater separation of the MCC particles by excess moisture [30].

Effect of moisture content on disintegration time and tablet porosity

Figure 8 shows the effect of moisture content on tablet disintegration time and porosity. For example, at 7.7% w/w moisture content (with MCC 3) using interactive mixing at low speed (300 rpm), the tablets had a disintegration time of 7±1s whereas those prepared from 1.2% moisture powders (using MCC 1) had a longer disintegration time of 39±2s ($P<0.05$), **Figure 8**(a).

The porosity results during interactive mixing, shown in **Figure 8** (a), were consistent with disintegration results as the increase in moisture content caused a significant increase in porosity and a sharp decrease in disintegration time (ANOVA, $p<0.05$). This suggested that the high amount of moisture content may have led to creating a freely moving environment of the particle that contributed to finding the most suitable compact configuration; while disintegration time was prolonged at low moisture content as the reduction of pores reduced the ability for water to penetrate and break up the tablet. Although tablets retained high porosity, which is important to enhance water penetration and disintegration of tablets, their hardness was insufficient at 14±3.3 N (**Figure 7** (a)). Additionally, increasing particle size range may have led to larger void spaces, which yielded a growth in porosity. Interestingly, when scanning electron microscopy (SEM) tests were carried out, it was recognized that a

571 small increase in particle size of the MCC 2 moisture content particles was observed
572 compared to MCC 1.
573
574 These increases in average particle size of the MCC 2 powders could be referred to as the
575 coalescence process, at which the particles combined to form big clusters. Therefore, it is
576 possible that the increased non-viscous binder (water) led to improved hardness, friability,
577 disintegration time and porosity of tablets as the increased moisture created free movement
578 for particles, increasing the consolidation process and decreasing the coalescence
579 processes[31].

580 ## Conclusion

581 Manufacturing powders with differing levels of moisture content resulted in an alteration in the
582 powder morphology as observed from SEM and AFM studies. This study showed that the
583 amount of moisture content within MCC affected the mechanical properties of the subsequent
584 powders and it was concluded that inclusion of 11% MCC moisture content resulted in the
585 most flowable powder with favourable ODT characteristics, as tablets displayed increased
586 hardness when formed using direct compression. Extreme moisture contents in pre-
587 processing materials could be reduced using varying process parameters using composite dry
588 coating, as well as mixing of the powders with excipients designed to dry coat the surface of
589 the high moisture content carrier particles. The understanding of tableting performance of
590 excipients at the particle level (nanoindentaion study) would facilitate the rational design of
591 ODT formulations through consideration of the main factors that contribute to high hardness
592 and fast disintegration which in turn would considerably accelerate product development.
593

594 **Conflict of interest**

595 The authors confirm that this article content has no conflicts of interest.
596

Acknowledgment

The authors would like to acknowledge the funding from Najran University (Saudi Arabia) for providing a full scholarship to support Hamad Alyami towards his PhD. Colorcon® Inc and Aston University are thanked for their financial support in funding Jasdip Koner. Eman Dahmash Is a recipient of overseas bursary funded by Aston University.

References

1. Turner, M., *et al.* Paediatric drug development: The impact of evolving regulations. *Advanced drug delivery reviews*. (2014). **73**: p. 2-13.
2. Kellie, S.J. and Howard, S.C. Global child health priorities: What role for paediatric oncologists? *European Journal of Cancer*. (2008). **44**(16): p. 2388-2396.
3. Ivanovska, V., *et al.* Pediatric drug formulations: A review of challenges and progress. *Pediatrics*. (2014). **134**(2): p. 361-372.
4. Nunn, T. and Williams, J. Formulation of medicines for children. *British journal of clinical pharmacology*. (2005). **59**(6): p. 674-676.
5. van Riet-Nales, D.A., *et al.* Acceptability of different oral formulations in infants and preschool children. *Archives of disease in childhood*. (2013). **98**(9): p. 725-731.
6. Siddiqui, M.N., *et al.* A short review on "a novel approach in oral fast dissolving drug delivery system and their patents". *Advances in Biological Research*. (2011). **5**(6): p. 291-303.
7. Parkash, V., *et al.* Fast disintegrating tablets: Opportunity in drug delivery system. *Journal of advanced pharmaceutical technology & research*. (2011). **2**(4): p. 223.
8. Yoshinari, T., *et al.* Moisture induced polymorphic transition of mannitol and its morphological transformation. *International journal of pharmaceutics*. (2002). **247**(1): p. 69-77.
9. Pabari, R. and Ramtoola, Z. Effect of a disintegration mechanism on wetting, water absorption, and disintegration time of orodispersible tablets. *Journal of Young Pharmacists*. (2012). **4**(3): p. 157-163.
10. Hirani, J.J., *et al.* Orally disintegrating tablets: A review. *Tropical Journal of Pharmaceutical Research*. (2009). **8**(2): p. 161-172.
11. Prescott, J.K. and Barnum, R.A. On powder flowability. *Pharmaceutical technology*. (2000). **24**(10): p. 60-85.
12. Vromans, H. and Lerk, C. Densification properties and compactibility of mixtures of pharmaceutical excipients with and without magnesium stearate. *International journal of pharmaceutics*. (1988). **46**(3): p. 183-192.
13. Pharmacopoeia, B. Appendix xvii a. *Particle size of powders. vV*. (2012).
14. Bowen, J., *et al.* On the calibration of rectangular atomic force microscope cantilevers modified by particle attachment and lamination. *Measurement Science and Technology*. (2010). **21**(11): p. 115106.
15. Zhu, W., *et al.* Bond and interfacial properties of reinforcement in self-compacting concrete. *Materials and structures*. (2004). **37**(7): p. 442-448.
16. Yang, J., *et al.* Dry particle coating for improving the flowability of cohesive powders. *Powder Technology*. (2005). **158**(1): p. 21-33.
17. Rowe, R.C., *et al. Handbook of pharaceutical excipients*. 7 ed, ed. R.C. Rowe. Vol. 7. 2012, London: Pharmaceutical Press.
18. Khan, K., *et al.* The effect of moisture content of microcrystalline cellulose on the compressional properties of some formulations. *Drug Development and Industrial Pharmacy*. (1981). **7**(5): p. 525-538.
19. Sarraguça, M.C., *et al.* Determination of flow properties of pharmaceutical powders by near infrared spectroscopy. *Journal of pharmaceutical and biomedical analysis*. (2010). **52**(4): p. 484-492.
20. Al-Khattawi, A., *et al.* Evidence-based nanoscopic and molecular framework for excipient functionality in compressed orally disintegrating tablets. (2014).
21. Al-Khattawi, A., *et al.* Systematic screening of compressed odt excipients: Cellulosic versus non-cellulosic. *Current drug delivery*. (2014). **11**(4): p. 486-500.
22. Crouter, A. and Briens, L. The effect of moisture on the flowability of pharmaceutical excipients. *AAPS PharmSciTech*. (2014). **15**(1): p. 65-74.
23. Dawoodbhai, S. and Rhodes, C.T. The effect of moisture on powder flow and on compaction and physical stability of tablets. *Drug Development and Industrial Pharmacy*. (1989). **15**(10): p. 1577-1600.
24. Shi, L., *et al.* Initial moisture content in raw material can profoundly influence high shear wet granulation process. *International journal of pharmaceutics*. (2011). **416**(1): p. 43-48.

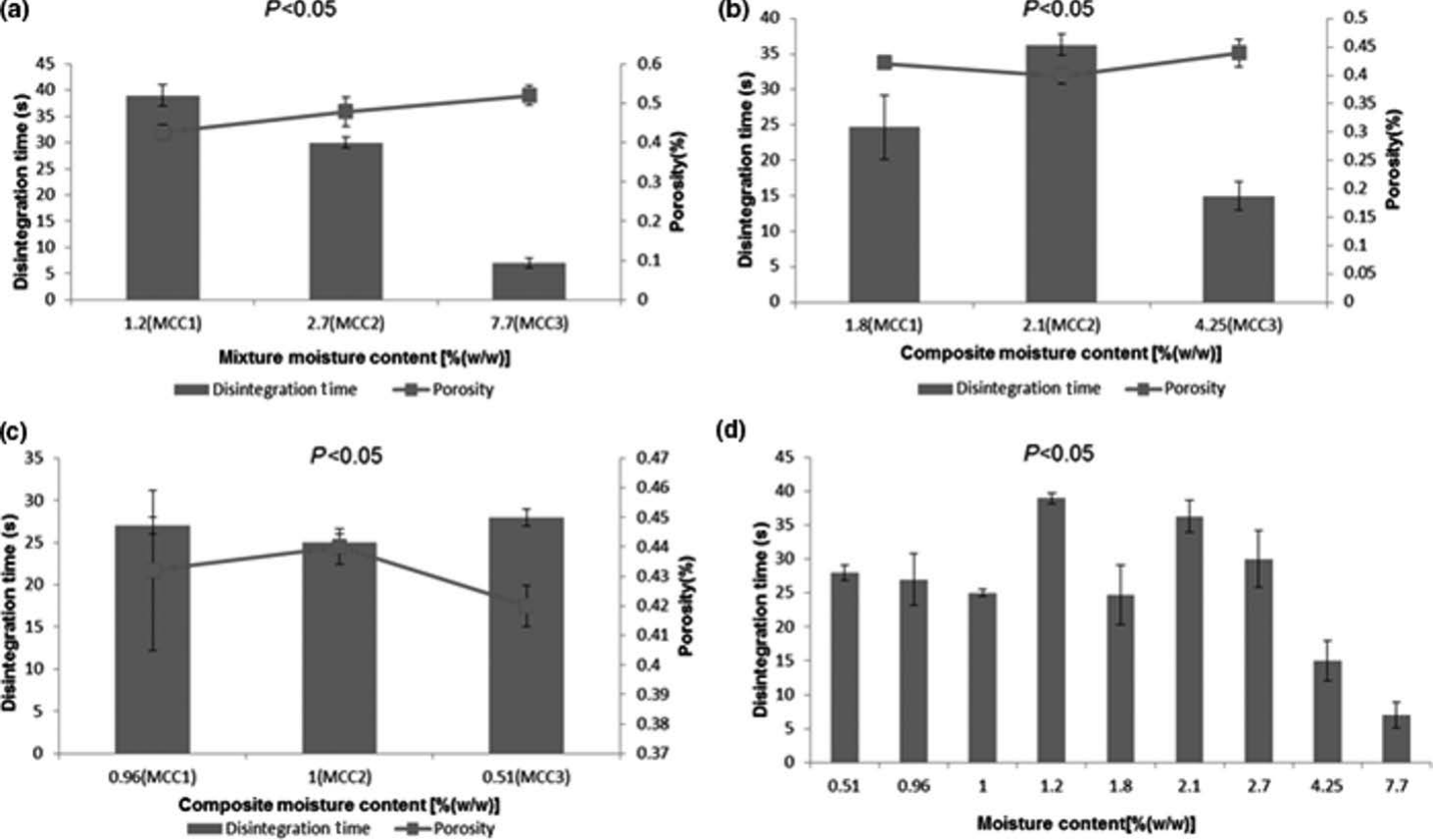
25. Karner, S. and Urbanetz, N.A. The impact of electrostatic charge in pharmaceutical powders with specific focus on inhalation-powders. *Journal of Aerosol Science*. (2011). **42**(6): p. 428-445.
26. Das, K., *et al.* A study of the mechanical, thermal and morphological properties of microcrystalline cellulose particles prepared from cotton slivers using different acid concentrations. *Cellulose*. (2009). **16**(5): p. 783-793.
27. Mujumdar, A., *et al.* Improvement of humidity resistance of magnesium powder using dry particle coating. *Powder Technology*. (2004). **140**(1–2): p. 86-97.
28. Koner, J.S., *et al.* A holistic multi evidence approach to study the fragmentation behaviour of crystalline mannitol. *Scientific reports*. (2015). **5**.
29. Tatavarti, A.S., *et al.* Evaluation of the deformation behavior of binary systems of methacrylic acid copolymers and hydroxypropyl methylcellulose using a compaction simulator. *International journal of pharmaceutics*. (2008). **348**(1): p. 46-53.
30. Nokhodchi, A., *et al.* The effect of moisture on the properties of ibuprofen tablets. *International journal of pharmaceutics*. (1995). **118**(2): p. 191-197.
31. Iveson, S.M., *et al.* Nucleation, growth and breakage phenomena in agitated wet granulation processes: A review. *Powder Technology*. (2001). **117**(1): p. 3-39.
32. Malamataris, S. and Pilpel, N. Tensile strength and compression of coated pharmaceutical powders: Tablets. *Journal of Pharmacy and Pharmacology*. (1983). **35**(1): p. 1-6.
33. Li, L. and Peck, G. The effect of moisture content on the compression properties of maltodextrins. *Journal of Pharmacy and Pharmacology*. (1990). **42**(4): p. 272-275.
34. Kristensen, H., *et al.* Mechanical properties of moist agglomerates in relation to granulation mechanisms part ii. Effects of particle size distribution. *Powder technology*. (1985). **44**(3): p. 239-247.
35. Brittain, H.G. *Physical characterization of pharmaceutical solids*. 1995: Marcel Dekker.

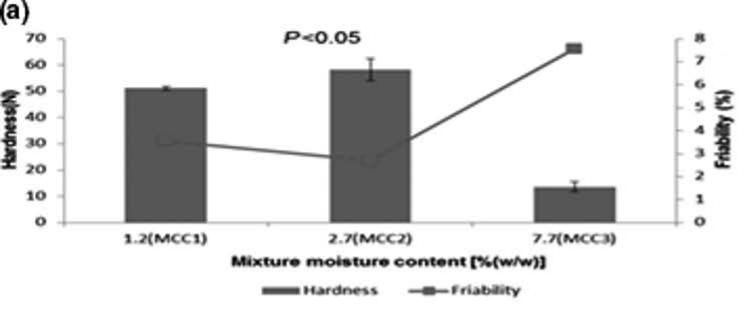
Table 1: Formulation content and processing parameters of MCC (carrier) and D-mannitol (guest) (mannitol particle size <38 µm) used for composite and interactive mix.

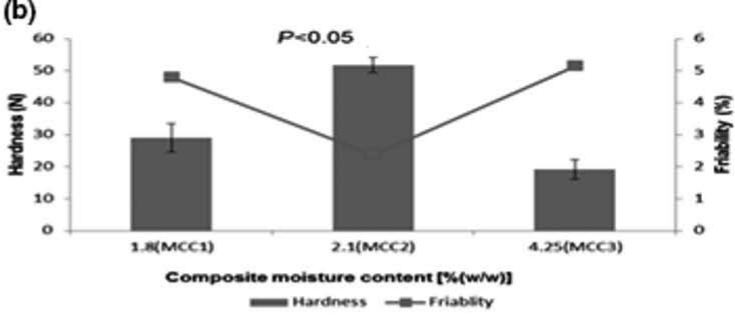
Formulation	Mannitol (%,w/w)	MCC (%,w/w)	Crospovi-done (%,w/w)	Mg stearate (%,w/w)	Mixing Technique	Duration (min)	Speed (rpm)	Air Pressure (PSI)	Batch size (g)
F1	64.5	30	5	0.5	Interactive	10	300	NO	10
F2	64.5	30	5	0.5	Composite	60	1500	NO	10
F3	64.5	30	5	0.5	Composite	60	1500	YES	10

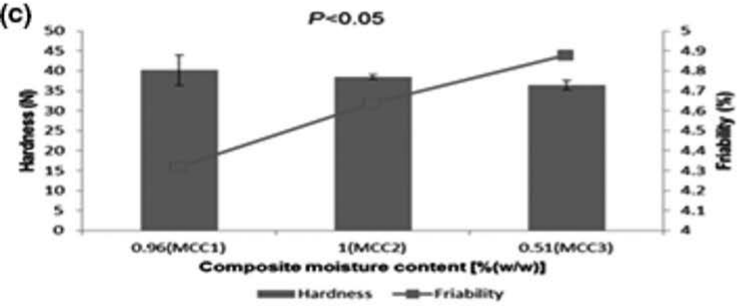
Table 2: Initial and final moisture contents for MCC at different processing parameters using powder coater (rpm: revolutions per minute)

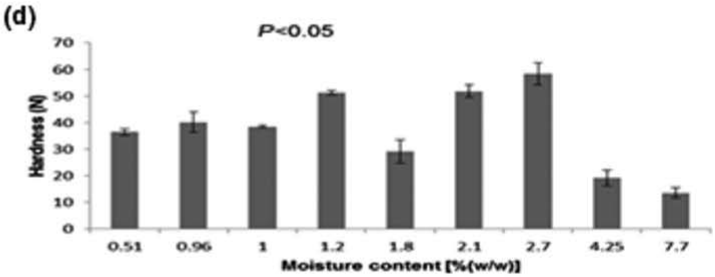
Initial MCC Powder moisture content %	Process Parameter	Final Moisture Content % Mean ± SD (n=3)
MCC1 (4%)	300rpm	3.7 ± 0.53
MCC 2 (11%)		9.16 ± 0.84
MCC 3 (40%)		37.7 ± 3.74
MCC1 (4%)	1500rpm	3.41 ± 0.02
MCC 2 (11%)		7.33 ± 0.93
MCC 3 (40%)		35.31 ± 0.93
MCC1 (4%)	1500rpm + air flow	1.28 ± 0.14
MCC 2 (11%)		2.96 ± 0.22
MCC 3 (40%)		8.38 ± 0.622

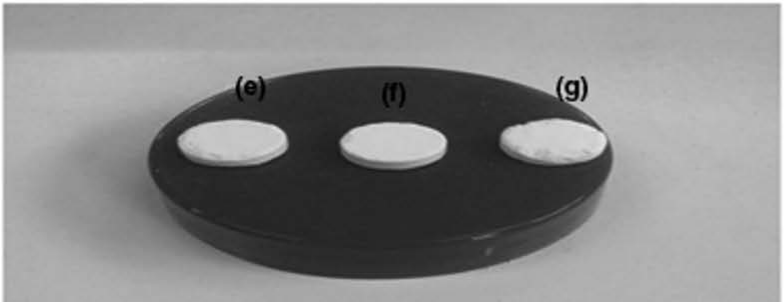

(a)
P<0.05
Disintegration time (s)
Porosity(%)
1.2(MCC1)
2.7(MCC2)
7.7(MCC3)
Mixture moisture content [%(w/w)]
Disintegration time
Porosity
(b)
P<0.05
Disintegration time (s)
Porosity(%)
1.8(MCC1)
2.1(MCC2)
4.25(MCC3)
Composite moisture content [%(w/w)]
Disintegration time
Porosity
(c)
P<0.05
Disintegration time (s)
Porosity(%)
0.96(MCC1)
1(MCC2)
0.51(MCC3)
Composite moisture content [%(w/w)]
Disintegration time
Porosity
(d)
P<0.05
Disintegration time (s)
0.51
0.96
1
1.2
1.8
2.1
2.7
4.25
7.7
Moisture content[%(w/w)]

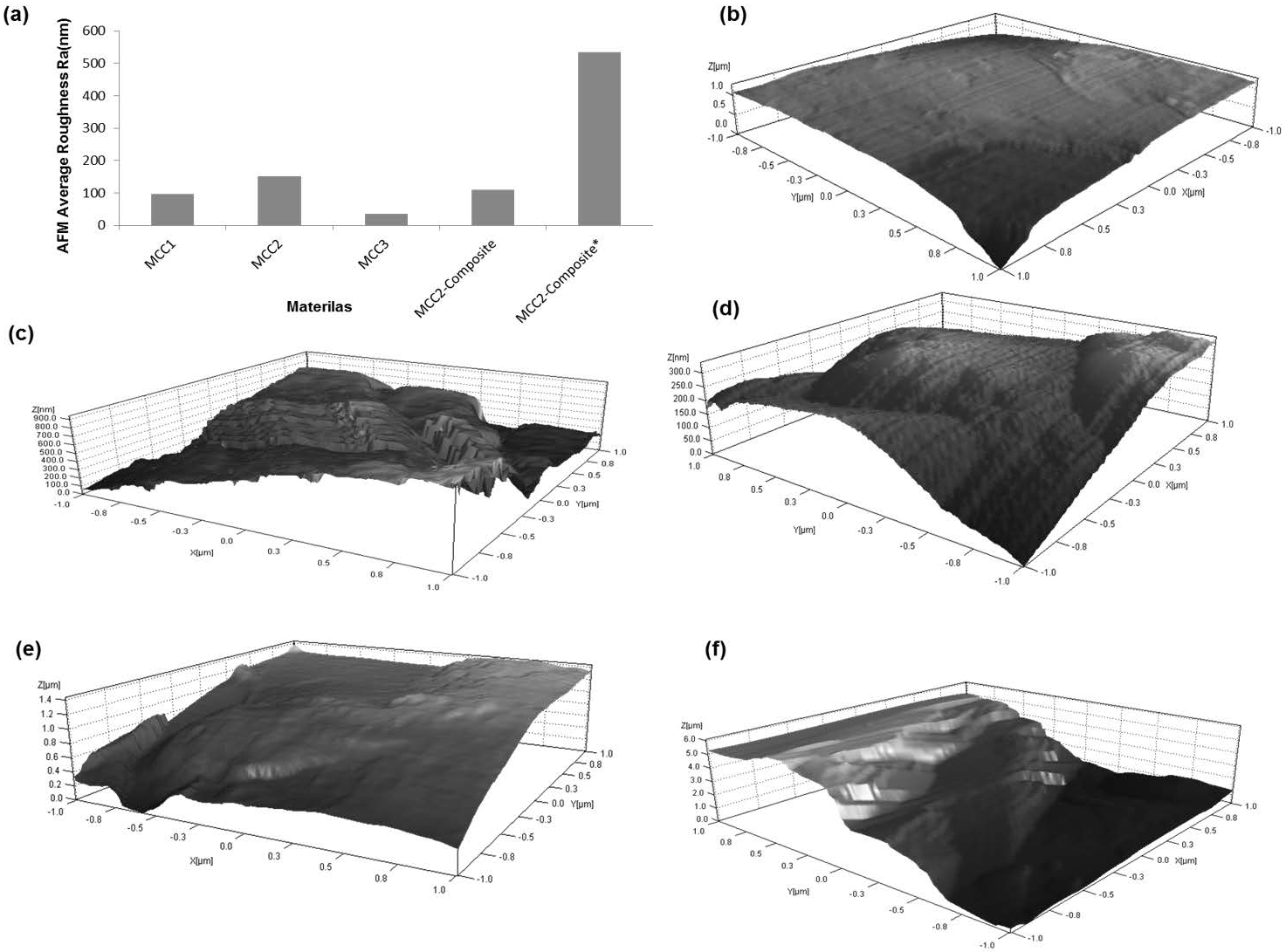

(a)
P<0.05
Hardness(N)
Friability (%)
1.2(MCC1)
2.7(MCC2)
7.7(MCC3)
Mixture moisture content [%(w/w)]
Hardness
Friability

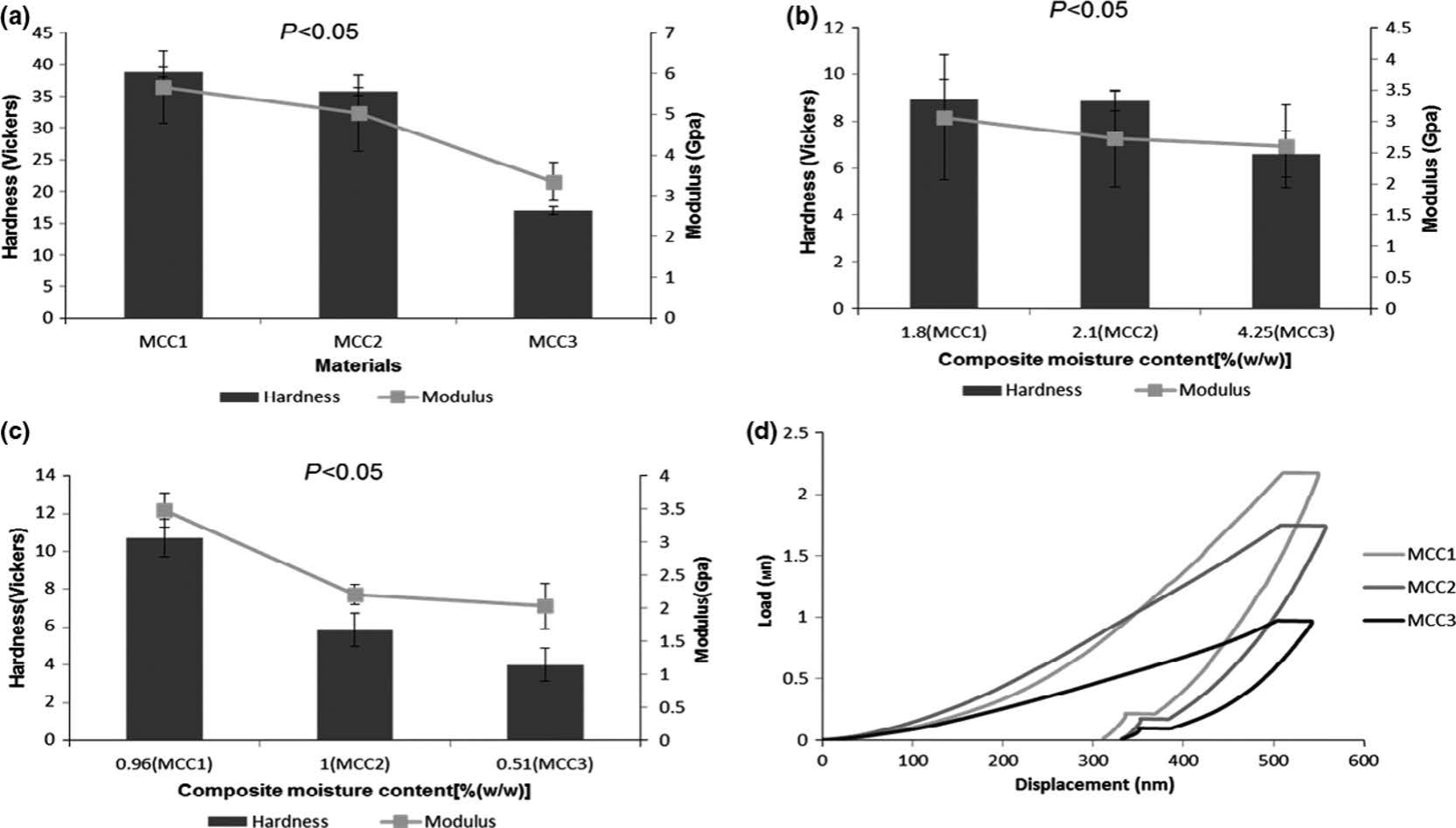

(b)
P<0.05
Hardness (N)
Friability (%)
1.8(MCC1)
2.1(MCC2)
4.25(MCC3)
Composite moisture content [%(w/w)]
Hardness
Friability

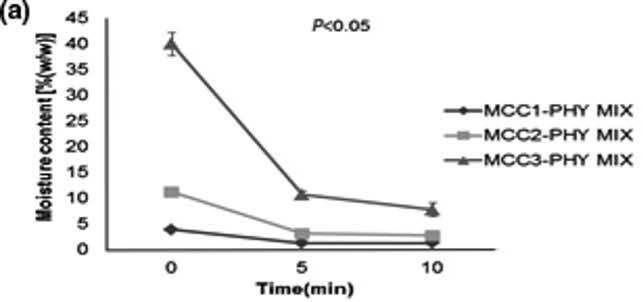

(c)
P<0.05
Hardness (N)
Friability (%)
0.96(MCC1)
1(MCC2)
0.51(MCC3)
Composite moisture content [%(w/w)]
Hardness
Friability

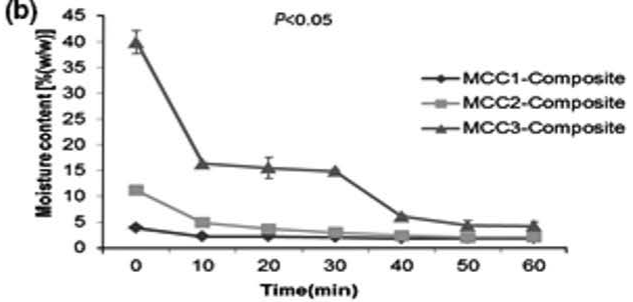

(d)
P<0.05
Hardness (N)
0.51
0.96
1
1.2
1.8
2.1
2.7
4.25
7.7
Moisture content [%(w/w)]

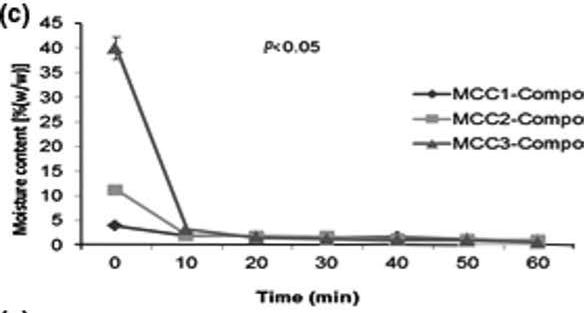

(e)
(f)
(g)

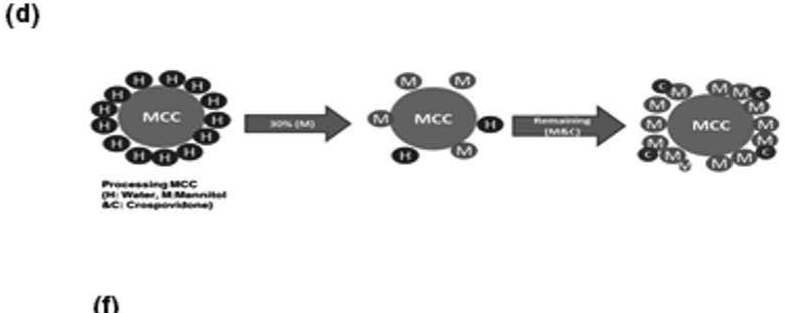

(a)
AFM Average Roughness Ra(nm)
600
500
400
300
200
100
0
MCC1
MCC2
MCC3
MCC2-Composite
MCC2-Composite*
Materilas
(b)
Z[µm]
Y[µm]
X[µm]
(c)
Z[nm]
X[µm]
Y[µm]
(d)
Z[nm]
Y[µm]
X[µm]
(e)
Z[µm]
X[µm]
Y[µm]
(f)
Z[µm]
Y[µm]
X[µm]

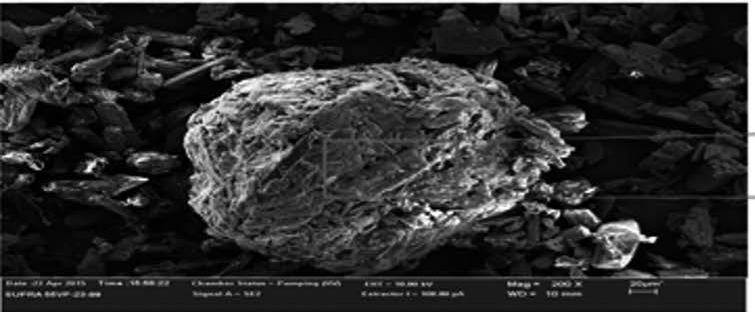

(a)
P<0.05
Hardness (Vickers)
Modulus (Gpa)
MCC1
MCC2
MCC3
Materials
Hardness
Modulus
(b)
P<0.05
Hardness (Vickers)
Modulus (Gpa)
1.8(MCC1)
2.1(MCC2)
4.25(MCC3)
Composite moisture content[%(w/w)]
Hardness
Modulus
(c)
P<0.05
Hardness(Vickers)
Modulus(Gpa)
0.96(MCC1)
1(MCC2)
0.51(MCC3)
Composite moisture content[%(w/w)]
Hardness
Modulus
(d)
Load (MN)
Displacement (nm)
MCC1
MCC2
MCC3

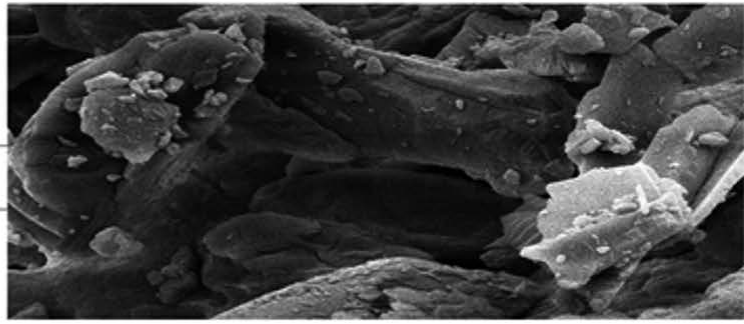

(a)
P<0.05
Moisture content [%(w/w)]
MCC1-PHY MIX
MCC2-PHY MIX
MCC3-PHY MIX
Time(min)

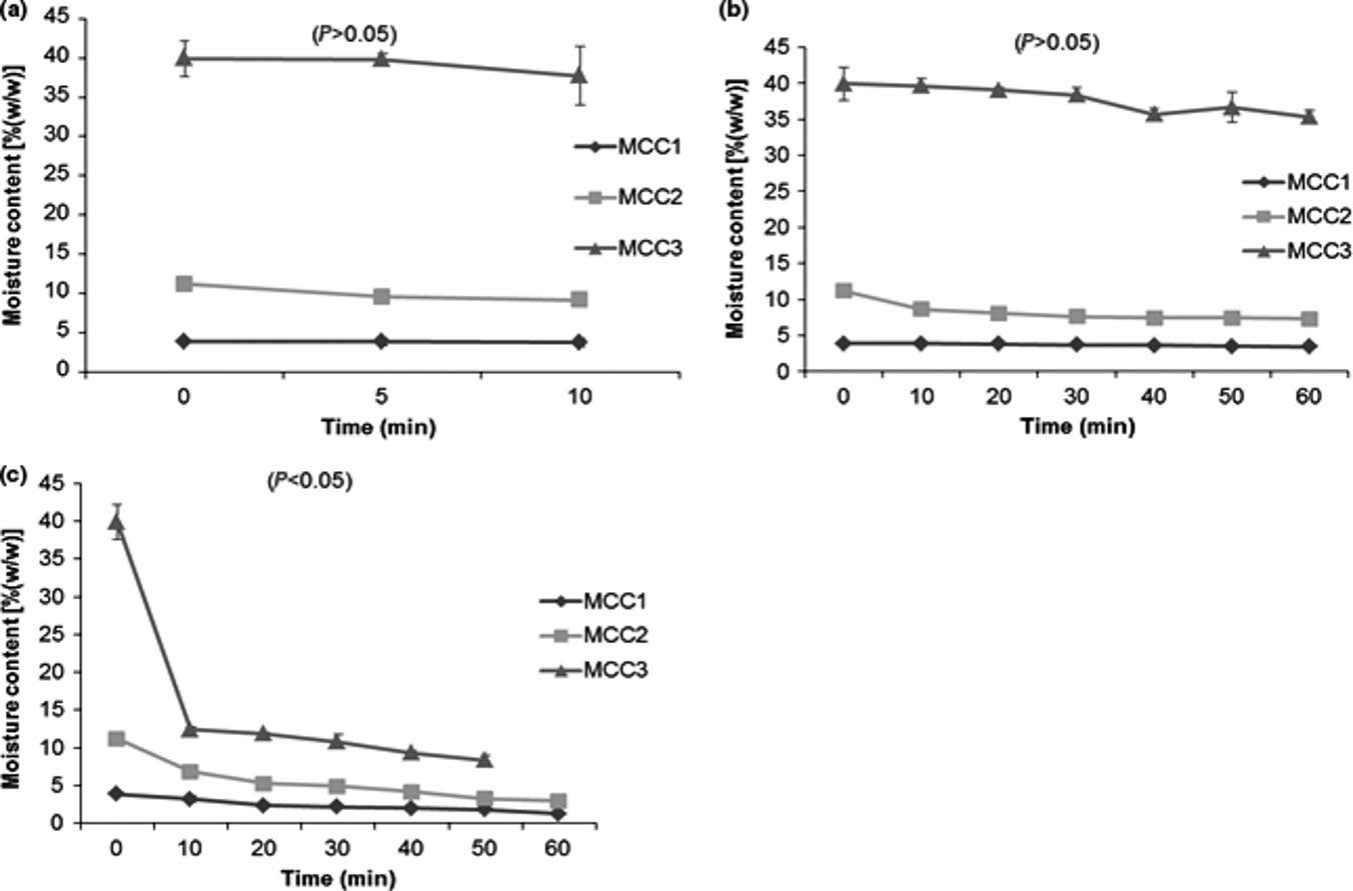

(b)
P<0.05
Moisture content [%(w/w)]
MCC1-Composite
MCC2-Composite
MCC3-Composite
Time(min)

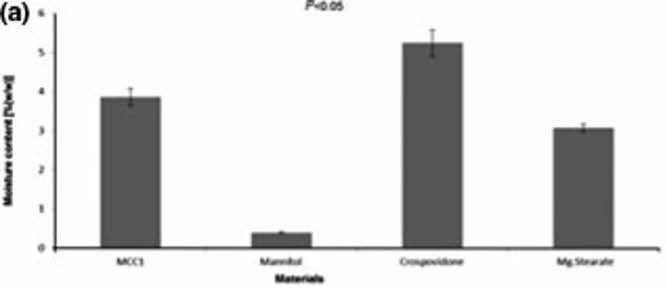

(c)
P<0.05
Moisture content [%(w/w)]
MCC1-Composite
MCC2-Composite
MCC3-Composite
Time (min)

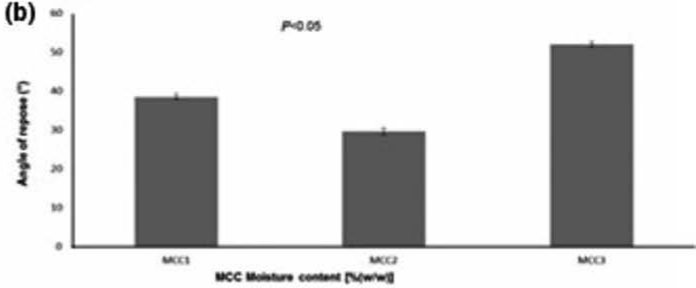

(d)
MCC
30% (M)
MCC
Remaining (MCC)
MCC
Processing MCC
(H: Water, M:Mannitol
&C: Crospovidone)

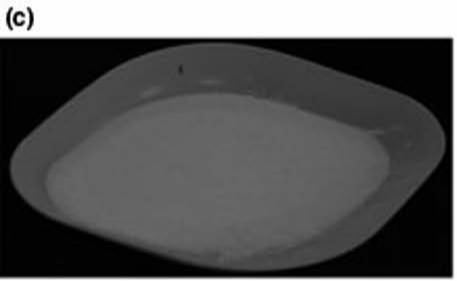

(e)

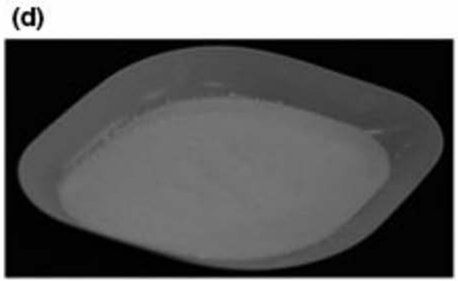

(f)

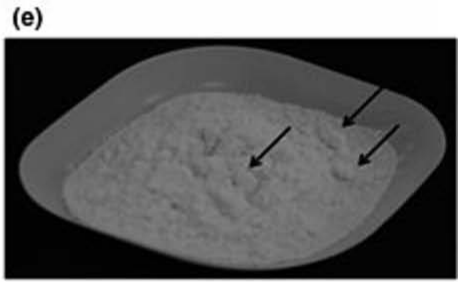

(a)
(P>0.05)
Moisture content [%(w/w)]
Time (min)
MCC1
MCC2
MCC3
(b)
(P>0.05)
Moisture content [%(w/w)]
Time (min)
MCC1
MCC2
MCC3
(c)
(P<0.05)
Moisture content [%(w/w)]
Time (min)
MCC1
MCC2
MCC3

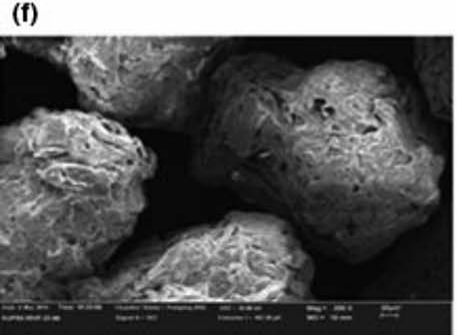

(a)
P<0.05
Moisture content [%(w/w)]
MCC1
Mannitol
Crosgovidone
Mg Stearate
Materials

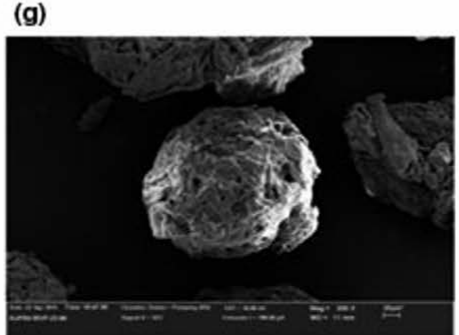

(b)
P<0.05
Angle of repose (°)
MCC1
MCC2
MCC3
MCC Moisture content [%(w/w)]

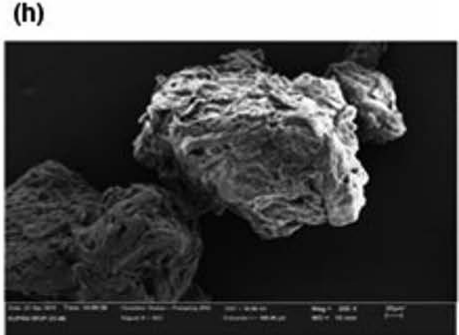

(c)

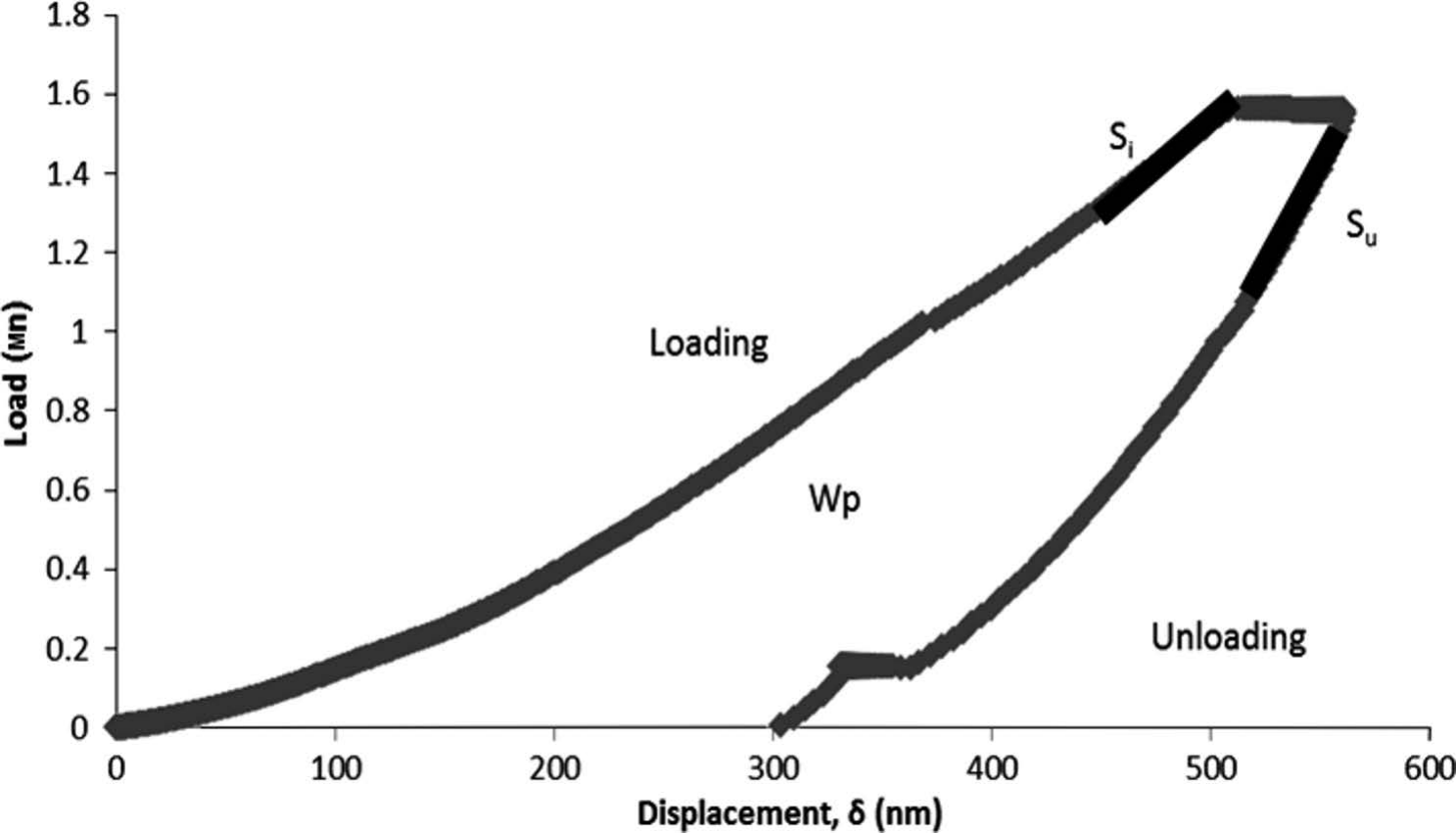

(d)


(e)


(f)


(g)


(h)


1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Load (Mn)
0
100
200
300
400
500
600
Displacement, δ (nm)
Loading
Unloading
Wp
S_i
S_u