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Mechanism of moisture induced variations in true density and compaction properties of microcrystalline cellulose

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Abstract

A single lot of MCC powder (Avicel PH102) was equilibrated at 0%, 11.35%, 21.6%, 38.2%, 52%, 57.5%, 75% and 84.3% relative humidity. Each equilibrated powder was compressed. Tablet density and tensile strength were measured as a function of pressure. Powder true density, tabletability, compressibility, compactibility and plasticity were obtained as a function of water content. The true density of MCC ranged 1.42–1.46 g/cm^3 and exhibited a maximum between ~3% and ~5% (wt%) moisture. Moisture up to ~3.3%, corresponding to monolayer coverage, did not induce profound change in MCC plasticity nor bonding strength despite reduced T_g. Consequently, the compaction properties were largely insensitive to moisture variation below 3.3% water. Above 3.3% water, higher moisture content corresponded to improved plasticity, due to the plasticizing effects of water above the critical water content, and consequently larger interparticulate bonding area when compressed. Effects of plasticization by water on bonding area were significant at low compaction pressures but diminish at higher pressures. At above 3.3% water, increasing moisture content also reduced bonding strength. Due to the interplay among the plasticity, compaction pressure and bonding strength, tablet tensile strength peaked in the range of 3.3–5.6% moisture.

Keywords: Microcrystalline cellulose; Compaction; Moisture; Antiplasticization; Plasticity; Tabletability; Compressibility; Compactibility

1. Introduction

Optimization of pharmaceutical solids for tablet manufacturing is often achieved by industrial processing, i.e., roller compaction, wet granulation and spray-drying. Structure–property relationship lies at the heart of successful materials engineering. Microcrystalline cellulose (MCC, Scheme 1) is one of the most commonly used tableting excipients in tablet formulation (Galichet, 2006). To understand the structure and properties of MCC, it is useful to first examine the processes used to produce it. MCC is manufactured by treating purified wood pulp using mineral acid solution. The treated wood pulp is then rinsed and spray-dried with or without additional process step, e.g., milling. Mineral acid cleaves the β-1,4 linkage between glucopyranose units of cellulose in the amorphous regions of cellulose particles (Iijima and Takeo, 2000). Consequently, the degree of polymerization of cellulose molecules decreases and levels off at a value, 200–300, defined by size of crystalline domains that are commonly termed microfibrils. Because of the partial removal of amorphous regions, the crystallinity of MCC is higher than that of pre-treated cellulose in wood pulp. However, because of the relatively small size of microfibril, 5–10 nm in width, a significant portion of cellulose molecules is exposed on the surfaces of cellulose microfibrils. Powder X-ray diffraction (PXRD) pattern of MCC shows characteristics of amorphous materials with the absence of intense sharp peaks probably due to a lack of long-range order of cellulose molecules on the two shorter dimensions of microfibril. Consequently, crystallinity of MCC is significantly below 100% by PXRD. A number of studies suggested that crystallinity of commercial MCC was 60–80% by PXRD (Doelker et al., 1987a; Nakai et al., 1977; Rowe et al., 1994). These crystallinity values are roughly in agreement with calculated % of cellulose molecules not on surfaces assuming a 5 and 10 nm width of microfibrils, respectively (the width of a cellulose molecular chain is 0.5 nm) (Iijima and Takeo, 2000; Verlhac and Dedier, 1990). MCC particles are birefringent under polarized light microscope and no amorphous region (area lacks birefringence) is evident suggesting its crystalline nature. Possibly,

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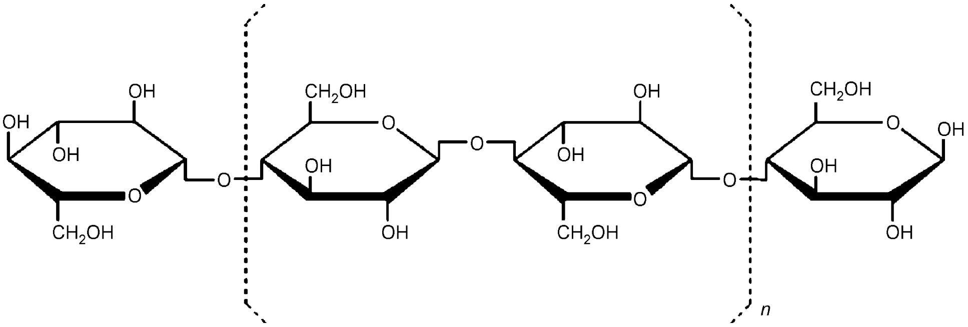

Scheme 1. Molecular structure of cellulose.

amorphous regions overlay with crystalline regions in the path of the polarized light and is difficult to be observed. Based on the discussion, the term "micro-crystalline" is well suited to describe the structure of MCC. The nano-crystalline nature of the MCC was supported by a recent study employing the Rietveld analysis.(Bates et al., 2006).

Owing to its imperative roles in tablet formulation development, physical properties of commercial MCC have been extensively studied with regards to batch-to-batch variations of the same grade, physical properties of different grades, crystallinity, etc. (Bassam et al., 1988; Dittgen et al., 1993; Doelker, 1993; Doelker et al., 1987b; Landin et al., 1993a,b; Podczeck and Révész, 1993). It has been suggested that dry amorphous MCC can exhibit three glass transition temperatures, T_g, ~133, ~160 and ~184 °C, and adsorption of water can reduce T_g (Picker and Hoag, 2002). Moisture at approximately 5% (wt%) level can reduce T_g of MCC to 25 °C (Amidon and Houghton, 1995).

MCC is hygroscopic because of the presence of abundant hydroxyl groups on cellulose chains (Scheme 1) and relatively large surface to volume ratio of microfibrils due to their small size (Iijima and Takeo, 2000). In-die yield pressure of MCC was found to decrease with increasing moisture content (Khan et al., 1988). It was also observed that tensile strength and elastic modulus initially increased with increasing moisture content but decreased with further increases in moisture content (Khan et al., 1988; Malamataris et al., 1991; Stubberud et al., 1996). However, a clear explanation of the interesting observations eluded the original researchers. (Amidon and Houghton, 1995) found that compaction pressure required to form compacts of 0.6 solid fraction decreased log-linearly with increasing moisture content. They also found that some tableting indices and powder flow properties of MCC were also dependent on moisture content. Viscoelastic properties of MCC compacts were also found to depend on amounts of moisture (Radebaugh et al., 1989). Previous studies focused on change of tablet properties either at a common compaction pressure or at a common porosity. For a given powder, porosity of a compact formed depends on compaction pressure. The relationship between porosity and compaction pressure is sometimes termed compressibility (Joiris et al., 1998; Sun and Grant, 2001b). Because compressibility of MCC powders depends on moisture content, the same pressure may not result in the same porosity and different pressures may be required to achieve the same tablet porosity. The use of a single tablet pressure or porosity in the previous studies only provides a slice of the complex response surface of tableting properties to moisture content. To understand the mechanism of water induced variations in mechanical properties of MCC, it is necessary to study effects of moisture content on tablet properties across a range of compaction pressures and tablet porosities.

This study differs from previous studies on this subject in two aspects. First, we considered both tensile strength and porosity at a number of pressures to obtain complete response surface of tableting properties to variations in moisture content. Secondly, we used a method that enabled us to obtain accurate true density of water-containing MCC (Sun, 2004, 2006). The use of helium pycnometry in the previous studies resulted in inaccurate true density for MCC because water released during measurement invalidated underlying assumption of constant number of molecules in gaseous phase during measurement. Impact of inaccurate true density on tableting data analysis can be profound (Sun, 2005b,c; Sun and Grant, 2001c). For example, a 1% error in true density can result in approximately 7% error in predicted tensile strength at approaching zero porosity for a typical pharmaceutical powder (Sun, 2005b). Because true density of MCC is dependent on water content (Sun, 2005c), true density for each water-containing MCC equilibrated at different relative humidity (RH) needs to be determined and used in corresponding data analysis. If a single true density value is used for MCC containing varying amounts of water, most of the relationship uncovered in this study would have been very difficult, if not impossible, to discern.

2. Materials and methods

2.1. Materials

A single lot of MCC (Avicel® PH102, FMC, lot K0200406) was equilibrated for at least 1 month over anhydrous calcium sulfate under vacuum (0% RH) and over a series of saturated inorganic salt solutions with 11.3% (LiCl), 21.6% (CH_3COOK), 38.2% (NaI), 52% ($Mg(NO_3)_2$), 57.5% (NaBr), 75% (NaCl) and 84.3% (KCl) RH, respectively. Each powder was transferred to a 40 mL scintillation vial immediately after the removal from equilibrating RH chamber and was sealed and stored in the same RH chamber.

2.2. Dynamic moisture sorption

The moisture sorption characteristics of MCC were assessed using about 15 mg of powder on an atmosphere-controlled microbalance (DVS Advantage 1, Surface Measurement Systems, Alperton, Middlesex, UK). The powder sample was dried on the balance by a stream of dry nitrogen gas purge at a rate of 100 mL/s until a stable weight was achieved. The sample was then subjected to a series of RH from 0% to 90% with a 3% RH increment. It was assumed that equilibrium was achieved when there was <0.5 μg weight increase in 10 min under a given RH.

2.3. Karl Fischer titrimetry (KFT)

The water content in each MCC sample was determined coulometrically using a Karl Fischer titrimeter (Model C3000 Titrator, AquaStar, EM Science). Three blanks were run by removing the stopper to the cell and by simulating the step of adding a sample to the cell but without using any powder. The average blank value was automatically registered and sample water content was automatically corrected using the blank value. The relative humidity around the titrimeter during the time of measurement was about 30%. Accurately weighed powder samples were transferred to the titration vessel. Three tests were performed for each sample to calculate average and the standard error of its water content.

2.4. Preparation of tablets

A set of round flat-faced tooling with a 10.00 mm diameter was used for compression. Punch faces and die wall were dusted with magnesium stearate prior to each compaction. An aliquot of each powder, 300–400 mg, was directly poured to die from vial in less than 3 s. The vial was sealed immediately after each transfer and stored in the same equilibration RH chamber to minimize exposure to ambient air. Compression force was applied using an instrumented hydraulic press. The rate of loading was controlled to bring the force to its peak value in ∼10 s. Each powder was kept under pressure for a total of 30 s before the pressure was removed. A total of 12–20 tablets were made for each powder. The KFT water content of each remaining MCC sample was measured immediately after compaction study as described earlier. The powder remained in the vial was exposed to ambient air for a total of less than 1 min prior to water content measurement. Ambient RH during the time of compaction was approximately 25% measured using a hand held hygrometer.

Tablets were ejected manually after each compaction and stored in a sealed vial placed in a corresponding RH chamber. Tablet weight, dimensions and breaking force were measured between 1 and 2 h after ejection. Each tablet was accurately weighed to 0.1 mg and the diameter and the thickness of each tablet were measured to 0.01 mm using a digital caliper (Model 62379-531, Control Company, Friendswood, TX). To obtain accurate measurements of tablet dimensions, tablet surfaces were brushed gently to remove loose particles and flashing on the edges of tablets was also carefully removed. Tablet density, ρ_{tablet}, was calculated from tablet diameter, thickness and weight. In this study, MCC formed intact tablets under all pressures.

2.5. Deriving powder true density

Non-linear regression (Origin® V7.0, OriginLab Corp. Northampton, MA) of tablet density and corresponding compaction pressure data yielded true density along with two other useful constants, $1/C$ and ε_c (Kuentz and Leuenberger, 1999; Sun, 2004). The constant $1/C$ is related to the plasticity of the material. The constant ε_c describes a critical porosity below which the powder bed exhibits significant mechanical strength. It is frequently observed that certain plastic materials, e.g., KBr, can be compressed into transparent discs or compacts under an adequate pressure. This corresponds to tablets with zero porosity. Beyond that point, further increase in compression pressure does not cause further increase in tablet apparent density after ejection. Consequently, a plateau may be observed on the plot of tablet density versus pressure. In that case, points in the plateau region were not included for regression.

2.6. Calculation of tablet porosity

The porosity of tablets, ε, was calculated using Eq. (1).

$$\varepsilon = 1 - \frac{\rho_{\text{tablet}}}{\rho_{\text{true}}} \tag{1}$$

where ρ_{true} is the true density of the material (Sun and Grant, 2001a).

2.7. Measurement of tablet strength

After tablet weight and dimensions were measured, breaking force (tablet hardness in kN) of the tablets was measured using a tablet hardness tester (Tablet Tester 6D, Schleuniger Pharmatron Inc., Manchester). To eliminate effects of different tablet thickness on strength estimation, tensile strength was calculated using Eq. (2).

$$\sigma = \frac{2F}{10^6 \pi D T} \tag{2}$$

In Eq. (2), σ is the tensile strength (MPa), F the breaking force (N), D the tablet diameter (m) and T is the thickness of tablet (m) (Fell and Newton, 1970).

3. Results and discussion

3.1. Moisture sorption isotherm

The moisture sorption isotherm of MCC at 25 °C collected using the atmosphere-controlled microbalance is shown in Fig. 1. Fitting the moisture sorption data (weight ratio of water to dry solid and corresponding water activity) to Guggenheim Anderson and De Boer (GAB) model (Eq. (3)) by non-linear regression yields $W_m = 0.0355 \pm 0.00021$,

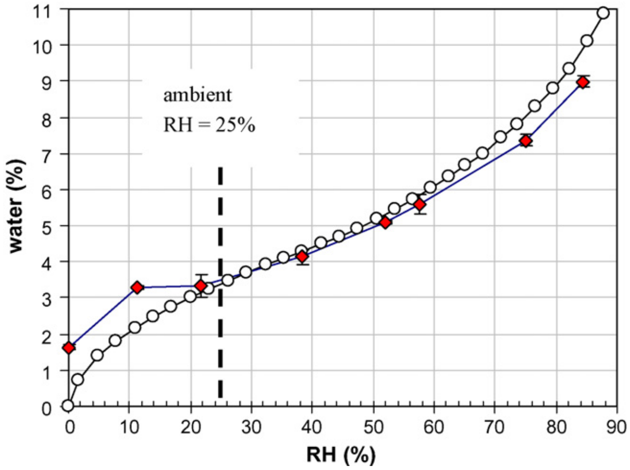

Fig. 1. Moisture content in MCC measured by: (a) static method using Karl-Fischer titrimetry (solid diamonds, $n = 3$) and (b) dynamic method using a humidity-controlled microbalance (open circles).

$C = 14.42 \pm 0.40$, $K = 0.814 \pm 0.002$, $R^2 = 0.9998$.

$$W = \frac{W_{\mathrm{m}} C K a_{\mathrm{w}}}{(1 - K a_{\mathrm{w}})(1 - K a_{\mathrm{w}} + C K a_{\mathrm{w}})} \qquad (3)$$

where W is the weight fraction of water to dry solid, α_{w} the water activity, W_{m} the amount of water corresponding to monolayer coverage, and C and K are parameters related to the heat of sorption of the monolayer and intermediate layers, respectively (Zografi et al., 1984).

The monolayer coverage $W_{\mathrm{m}} = 0.0355$, corresponding to 3.43% (wt%) moisture in the sample, is achieved at 0.26 partial water vapor pressure (26% RH) at 25 °C. The result is comparable to the literature data (Zografi et al., 1984). It should be pointed out that water present up to W_{m} is tightly bound to cellulose molecules (Zografi et al., 1984). For typical crystalline powders with particle size distribution similar to MCC Avicel PH102 ($d_{50} = 115\ \mu\mathrm{m}$), the water required for monolayer coverage is much less than 3.43%. The high W_{m} value suggests water can penetrate inside of the relatively porous MCC particles, probably covering surfaces of microfibrils in MCC and/or being concentrated in amorphous regions. This concept is supported by the observation that similar W_{m} values were obtained for MCC with different particle size distributions (Avicel PH101, $d_{50} = 84$ m, $W_{\mathrm{m}} = 0.0362$ (Amidon and Houghton, 1995) and Avicel PH200, $d_{50} = 209\ \mu\mathrm{m}$, $W_{\mathrm{m}} = 0.0348 \pm 0.0004$). To further probe the location of water in MCC, a suspension of MCC in water (4 g/10 mL) was prepared. After overnight, the suspension became a white paste. Evidently, most liquid water penetrated inside of the MCC particles. However, PXRD pattern of the paste was virtually identical to that of the dry MCC powder despite the profound change in texture and appearance of the suspension. This confirmed the structure of crystalline microfibrils was not altered by water and profound changes in physical properties of MCC were results of interactions between water and amorphous cellulose.

KFT water content in each MCC sample after powder compaction experiment is also plotted in Fig. 1. The two isotherms cross between 24% and 32% RH, corresponding to the ambient RH (25%) during powder compaction. By comparing the two sets of data, it is clear that powders equilibrated at 0% and 11.3% RH picked up much water from air during the process of powder compaction despite the relative short exposure to air. On the other hand, powders equilibrated at >32% lost some water to air during the same process. The sorption of water by MCC equilibrated at 0% and 11.3% RH during the experiment is much faster than desorption of water from MCC equilibrated at 39% RH and above (Fig. 1). Significant desorption of moisture only occurs for MCC equilibrated at 75% and 84.3% RH. Because of the relatively rapid change of moisture content in the four MCC samples, it is not appropriate to correlate the thermodynamic parameter, equilibrating water activity or RH, to changes in mechanical properties. Instead, water content in MCC immediately after tableting measured using KFT is used for that purpose.

3.2. *True density as a function of water content*

Fig. 2 shows true density of MCC as a function of water content. Clearly, MCC true density is not constant across the range of water content. MCC true density increases initially with increasing water content up to 3.3%. Between 3.3% and 5.1% water, true density remains constant at ∼1.46 g/cm^3. At higher water contents (5.1–9.0%), true density decreases with increasing amount of water in accord with the well-known swelling propensity of cellulose at high humidity. True density values reported here are lower than those calculated from crystal structures of perfect cellulose (1.56 and 1.61 g/cm^3 for I_α and I_β polymorphs, respectively). This is consistent with the fact that MCC is not 100% crystalline. The initial increase of true density may be explained by the antiplasticization effects of water on amorphous polymers (Dlubek et al., 2002). The antiplasticization is present when adsorbed moisture tightly bounds with disordered polymer chains, without causing significant expansion of the solid, to cause a net reduction of the free volume in amorphous polymers. This phenomenon was demonstrated in a positron lifetime study of polyamide 6 (Dlubek et al., 2002). Amorphous MCC containing less than 3.3% water remains

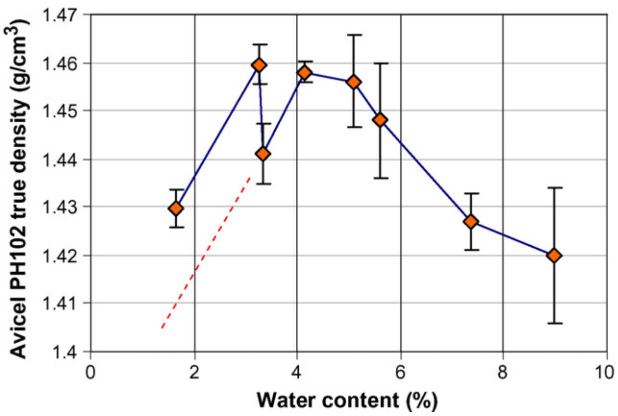

Fig. 2. True density of MCC as a function of water content. The broken line indicates the expected true density of MCC free from moisture exchange between MCC and air.

in glassy state at room temperature (Amidon and Houghton, 1995). In this region (<3.3% water), anti-plasticization effect of water resulted in reduced free volume of MCC with increasing water content, corresponding to the increasing true density of MCC (Fig. 2). Both cellulose and polyamide 6 polymer chains can form hydrogen-bonds with water, thus possessing a structural basis for the antiplasticization phenomenon, where water molecules are tightly bound to polymer chains and may be viewed as an integral part of the polymers. At higher water content region, more water results in larger free volume of the polymer–water mixture, expansion of the solid and reduced density because of the plasticizing effect of water. The shape of the true density – water content plot of MCC is approximately a mirror image of free volume – water content profile of polyamide 6 (Dlubek et al., 2002). True density values obtained here are 4–18% lower than literature values (1.512–1.668 g/mL) determined using helium pycnometry (Galichet, 2006). This is principally because of the inability of helium pycnometry to accurately measure true density of water-containing solids (Sun, 2004, 2005c, 2006). It should be noted that the effect of water on true density of MCC is attributed to the presence of ∼20–40% amorphous cellulose content. Since water only interacts with a cellulose single crystal on its surfaces, changing equilibrium RH does not have significant effect on true density of 100% crystalline cellulose. If stable pure amorphous cellulose is available, more profound effect of water on its true density may be expected. Because calculated crystal density of 100% crystalline cellulose is higher than true density of MCC, the true density of the pure amorphous cellulose should be substantially lower than corresponding MCC at identical water content.

The equilibrium water content for MCC at 0% and 11.3% RH is 0% and 2.2%, respectively, according to the DVS data (Fig. 1). However, the water content increased to 1.63% and 3.3% after a total of less than 1 min of exposure to a 25% RH air (Fig. 1). Therefore, the rate of water sorption from air by dry MCC is very fast. The swollen of MCC is negligible within the time frame of this study when compared to the rate of water adsorption by MCC. As a result, the transit true density obtained in this study for the two powders was higher than respective equilibrium true density. Corrected for this effect, a smoother relationship should be obtained (shown as the broken line in Fig. 2). Regretfully, we were not equipped to conduct study under controlled ambient RH to verify this.

3.3. *Terminology for describing powder compaction properties*

Compaction properties of MCC are systematically assessed based on tabletability (tensile strength versus compaction pressure), compressibility (porosity versus compaction pressure) and compactibility (tensile strength versus porosity). Underlying mechanisms to the changed compaction properties are further explored from the angles of bonding strength and powder plasticity. Terminologies different from the system adopted in this work had been used in the literature to describe powder compaction properties. In most of other terminologies, the three variables, pressure, porosity and tensile strength, critical to in-depth understanding of powder compaction are not simultaneously considered. Confusion in terminologies was sometimes caused when researchers termed relationship between different pairs of variables (e.g., tensile strength versus pressure, porosity versus pressure, ln(porosity) versus pressure, indentation hardness versus pressure) the same, e.g., compactibility. Other times, the same relationship was given different names (compactibility and compressibility for the tensile strength vs. pressure relationship) by different researchers. The current terminology was first defined by Joiris et al. (1998). A principal advantage of this system is the simultaneous consideration of interrelationships among all three critical variables. Many insights can be obtained by this type of data analysis. When the three variables are simultaneously considered, it has always been consistently used in the literature (Joiris et al., 1998; Sun, 2006; Sun and Grant, 2000, 2001a,b, 2004; Tye et al., 2005).

3.4. *Effects of water content on tabletability*

Tabletability describes strength a tablet attains under a given pressure. Thus, the knowledge of tabletability of any given powder is of practical importance in the formulation and process development (Sun and Himmelspach, 2006). Tabletability of MCC powders that contain different amounts of moisture differs significantly (Fig. 3a). When the pressure is higher than 100 MPa, tabletability of MCC equilibrated at 21.6% and 38.2% is higher than other powders equilibrated at either lower or higher RH. Tabletability of MCC equilibrated at 84.3% is the lowest in this study. Under identical compaction pressure, the highest tablet tensile strength is more than two-fold of the lowest tablet tensile strength. Dependence of tablet tensile strength on moisture is more clearly shown in Fig. 3b. Under a common pressure, tablet tensile strength is optimum at intermediate water content. For example, at 200 MPa tensile strength jumps at approximately 3.3% water after a relatively constant region below 3.3% water and then decreases gradually. Our results in general agree with observations noted by previous researchers (Khan et al., 1988; Malamataris et al., 1991; Stubberud et al., 1996). The results support specifications of “no more than 5%” MCC moisture content set in USP monograph since tabletability of MCC containing >5% moisture corresponds to poorer tabletability. Except for certain special grades of MCC, e.g., Avicel PH112, a typical lot of MCC contains ∼3% to ∼4% moisture falling in the range of optimum tabletability. The optimum tabletability of MCC can be maintained during usual manufacturing process if RH is kept between 20% and 50%, corresponding to 3.3% and 5% water, respectively.

3.5. *Effects of water content on compressibility*

Compressibility describes how porosity of a powder changes under pressure. With increasing pressure, density of a powder generally increases leading to decreasing porosity. The dependence of tablet density on pressure typically follows a modified Heckel equation (Kuentz and Leuenberger, 1999; Sun, 2004). With increasing pressure, tablet density approaches the true

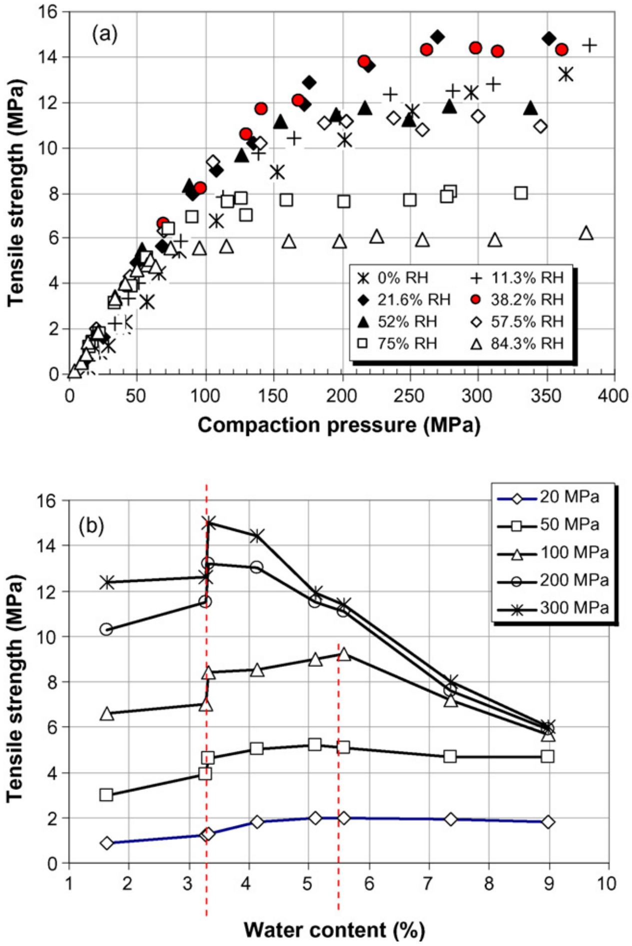

Fig. 3. Tabletability plots of MCC powders equilibrated at various relative humidities: (a) tablet tensile strength as a function of compaction pressure for each powder and (b) tablet tensile strength at selected compaction pressures as a function of water content.

density of the powder and tablet porosity approaches zero. For more plastic powders, tablet density generally approaches zero porosity faster because they undergo more permanent plastic deformation to more effectively eliminate pores under identical compaction conditions. For a given powder, lower tablet porosity results in larger areas of interparticulate bonding thus stronger tablet. When tablet porosity reaches zero under a certain pressure, further increase of pressure does not lead to larger bonding area between particles. Thus, no increase in tablet mechanical strength is resulted. This corresponds to a plateau region at high pressures on the tabletability plot (Fig. 3a).

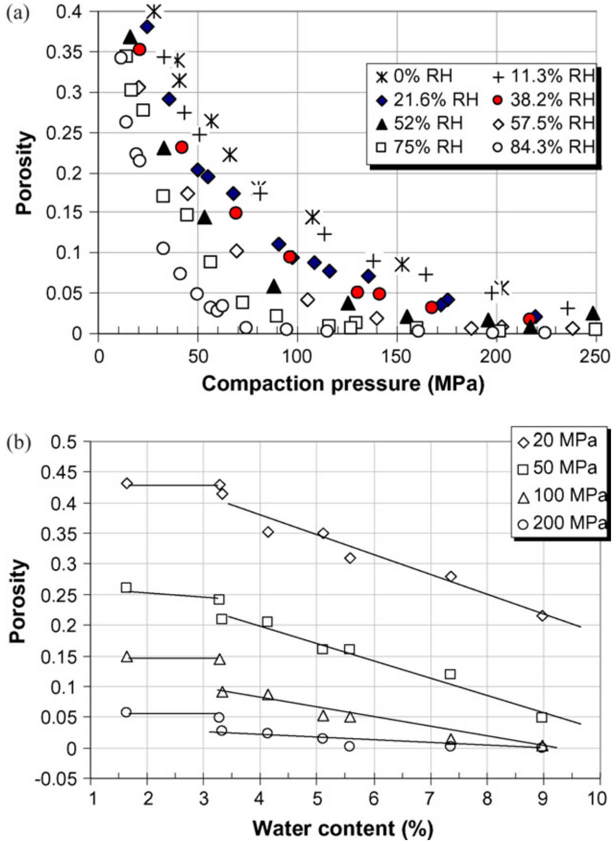

Fig. 4. Compressibility plots of MCC powders equilibrated at different relative humidities: (a) tablet porosity as a function of compaction pressure for each powder and (b) tablet porosity at selected compaction pressures as a function of water content.

Compressibility plots of MCC containing various amounts of moisture are presented in Fig. 4a. When water percentage is below monolayer coverage, change in water content does not result in significant change in compressibility since the compressibility plots are nearly identical for MCC containing 1.6% and 3.3% water. Above monolayer coverage (>3.3%), MCC approaches zero porosity faster with increasing moisture content (Fig. 4a). This can be more easily seen on Fig. 4b. The results suggest that MCC containing more moisture is more plastic. Plasticity of a powder may be assessed using $1/C$, with a unit of MPa, that can be obtained from the fitting tablet density vs. pressure data to the modified Heckel equation (Kuentz and Leuenberger, 1999; Sun, 2004, 2005a,c, 2006). The parameter, $1/C$, is analogous to the more familiar “mean yield pressure” obtained from a Heckel analysis of porosity vs. pressure data (Hersey and Rees, 1971; Hersey et al., 1973). A lower $1/C$ corresponds to a better plasticity. As shown in Fig. 5, $1/C$ is essentially constant at <3.3% water but decreases (plasticity

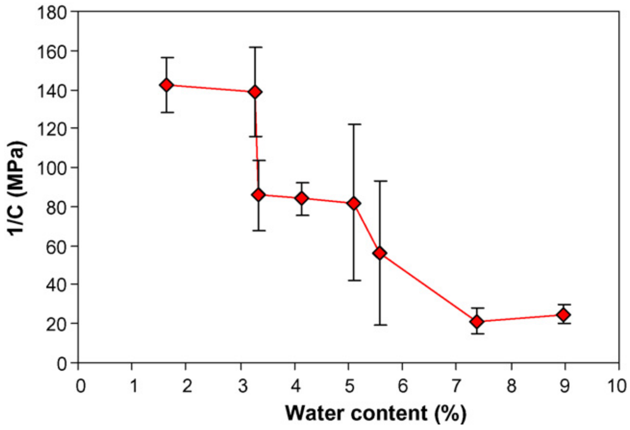

Fig. 5. With increasing water content, MCC becomes more plastic as indicated by decreasing $1/C$. A lower $1/C$ generally indicates a better deformability and the material is more plastic.

increases) sharply with increasing moisture content (six-fold reduction in $1/C$). However, higher moisture does not further plasticize MCC when >7% water is present (Fig. 5). The $1/C$ of MCC powders containing ∼7.4% and ∼9% moisture are not statistically different ($p > 0.05$). Above 3.3% level, the plasticizing effect of water on MCC is a result of the reduction in T_g corresponding to the increased free volume and mobility of cellulose chain. It is fundamentally different from the role water plays in improving plasticity of *p*-hydroxybenzoic acid monohydrate crystal, where water molecules separate and lubricate (similar to ball bearings) zigzag shaped layers in the crystal to facilitate plastic deformation (Sun and Grant, 2004).

3.6. Effects of water content on compactibility

Compactibility is represented by a plot of tablet tensile strength versus porosity (Fig. 6a). Typically, tensile strength decreases exponentially with increasing porosity. The tablet tensile strength versus porosity data is commonly analyzed using the Ryshkewitch equation (Ryshkewitch, 1953).

$$\sigma = \sigma_0\,\mathrm{e}^{-b\varepsilon} \tag{4}$$

where ε is the tablet porosity and σ is the tablet tensile strength. Constant σ_0 is the maximum tensile strength at zero tablet porosity and b is an empirical constant. Correlation coefficient of the non-linear regression, R^2, is greater than 0.98 in all cases in this study.

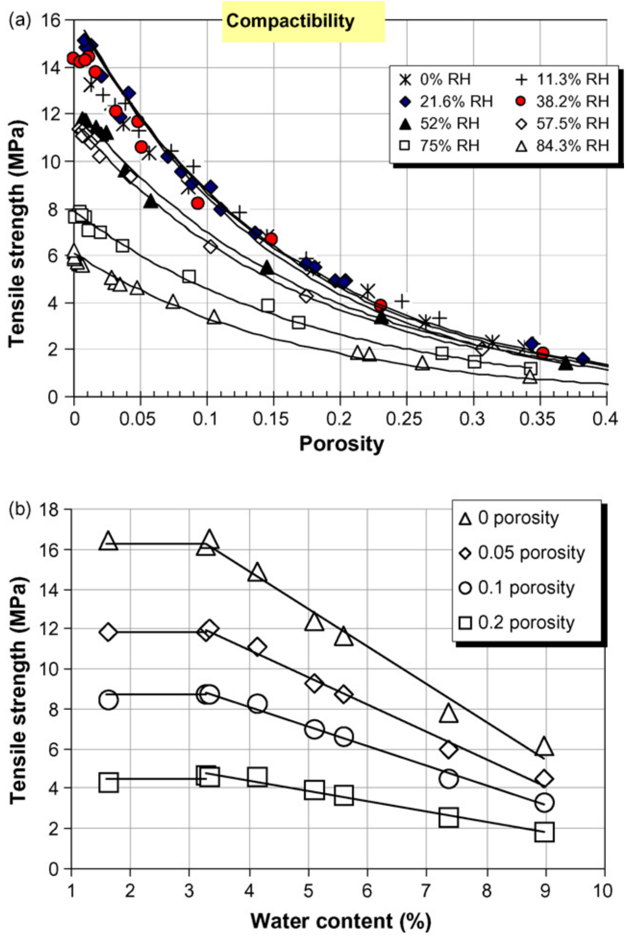

Fig. 6. Compactibility plots of MCC equilibrated at different relative humidities: (a) tablet tensile strength as a function of porosity for each powder and (b) tablet tensile strength at selected porosities as a function of water content.

Because a common batch of MCC is used in this study, particle size distribution, particle morphology, between any two powders are nearly identical. Consequently, bonding pattern in tablet of identical porosity is expected to be similar for MCC containing different amounts of moisture. Thus, tablet tensile strength at a common porosity, e.g., almost zero porosity, can be used to evaluate effects of moisture on bonding strength per unit bonding area. As shown in Fig. 6b, tablet tensile strength at a common porosity remains approximately constant up to the monolayer coverage (∼3.3% moisture). However, with further increase of moisture, tablet tensile strength decreases linearly, indicating the presence of more moisture reduces bonding strength. The observed insensitivity of bonding strength to water content below monolayer coverage implies the insertion of up to two layers of water between adjacent MCC surfaces does not significantly reduce the rigidity of the hydrogen-bonding network between surfaces. However, when more layers of water are present, the water is more fluid-like to cause lower bonding strength.

The constant b has been related to pore distribution within a tablet (Roberts et al., 1995; Sun and Grant, 2001a, 2004). Because a common batch of MCC is used in the present study, pore distribution in tablets should be similar. However, b varies with moisture content as shown in Fig. 7. The results suggest that constant b is also affected by factors other than pore distribution, for example, plasticity of the powder. Since b is the slope of the ln(tensile strength) versus porosity line, the higher b of MCC containing ∼9% water corresponds to faster increase in tensile strength as porosity is reduced.

3.7. Interplay among compaction pressure, bonding strength and plasticity

The existence of peak tensile strength at intermediate moisture contents is interesting (Fig. 3b). Similar behavior was noted

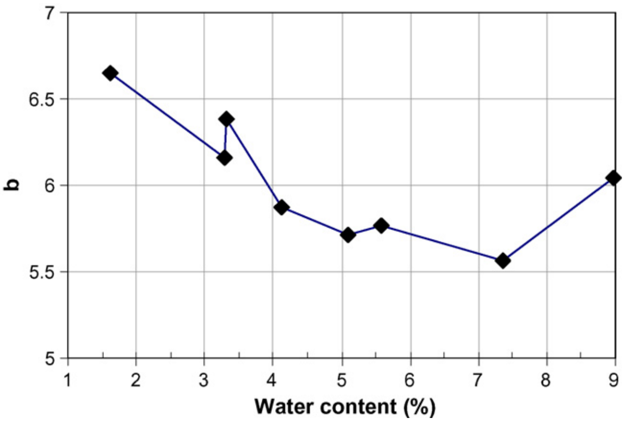

Fig. 7. Dependence of pre-exponential factor, b, in the Ryshkewitch equation on water content.

for MCC but a clear explanation eluded the original researchers (Khan et al., 1988; Malamataris et al., 1991). This phenomenon may now be understood with our ability to assess bonding strength (compactibility) and bonding area (compressibility) in this study. Below 3.3% water, variations in water content do not significantly affect bonding strength and plasticity as discussed previously. Consequently, tablet tensile strength is insensitive to variations in water content in this range. Above 3.3%, water plasticizes MCC sufficiently to make it more deformable under pressure. Under identical compaction conditions, MCC containing more moisture corresponds to tablets with lower porosity and therefore larger bonding area. Because of the high strength of cellulose chains in MCC, fracture plane in tablet is along the surface of MCC particles but not through them. Consequently, larger bonding area would correspond to stronger tablets if bonding strength is the same. This effect is more profound at low pressures than at high pressures. Under sufficiently high pressure, e.g., 200 MPa, porosity tends to approach zero for most MCC powders (Fig. 4b), despite their different plasticity (Fig. 5). Consequently, difference in plasticity does not translate into different bonding area thus exerting limited influence on tablet tensile strength. At pressures 100 MPa or below, the effect of increased bonding area initially outplays the effect of reduced bonding strength on tablet tensile strength. We see an increase in tensile strength with increased water content, between 3.3% and 5.6% (Fig. 3b). Above 5.6% water, the bonding strength is much more reduced with increased water content (Fig. 6b). This effect outplays the effect due to increased bonding area. Consequently, tensile strength decreases with increasing water content (Fig. 3b). At pressure of 200 MPa or greater, tablet porosity is close to zero for MCC containing varying amounts of water (Fig. 4b). Difference in bonding area is small despite significantly different plasticity. Thus, effect of water on bonding strength dictates the change in tensile strength. Consequently, tensile strength decreases with increasing water content due to the decreased bonding strength (Fig. 6b).

4. Conclusions

Due to the anti-plasticization effects of water, at below 3.3% (RH < 30%), adsorbed water fills free volume and increases true density of MCC but does not cause significant change in plasticity or bonding strength. As a result, tableting properties of MCC are insensitive to variation in water content in this range. However, at higher water content, tableting properties of MCC can be sensitive to variation in moisture content. The sensitivity at >3.3% water may be understood by simultaneously considering the effect of adsorbed water on MCC plasticity and interaction strength between bonding surfaces at various pressures. For robust and reproducible tableting results, it is advisable to maintain reasonably constant mechanical properties of MCC by avoiding extreme RH in manufacturing facilities. A systematic investigation of whether the same mechanisms may exist in other pharmaceutically important polymeric excipients is being pursued in our laboratory.

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