Comparative evaluation of silicified microcrystalline cellulose II as a direct compression vehicle

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ARTICLE INFO

ABSTRACT

The powder flow and tableting properties of novel silicified microcrystalline cellulose II (SMCCII) were evaluated and compared with current silicified cellulosic I excipients such as ProSolv® SMCC50 and ProSolv® SMCC90. This excipient was prepared by coprocessing cellulose II and silicon dioxide (SiO_2) at a 95:5 ratio by spray drying. The novel SMCCII yielded more benefits in terms of functionality as compared with the parent cellulose II material. SMCCII had higher bulk and tap densities, better powder packing ability, reduced porosity, increased surface area, and increased flowability. This silicified excipient had the highest brittleness behavior as given by the Heckel, Leuenberger and brittle fracture index analyses. The mechanical properties of SMCCII, such as toughness and Young's modulus were comparable to those of commercial products. SMCCII was the least sensitive material to magnesium stearate, and blending time or reprocessing did not affect its compactibility. It also provided for the fastest compact disintegration and release of griseofulvin. This new material has the potential for use as a direct compression excipient.

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1. Introduction

Microcrystalline cellulose (MCCII) was recently introduced as a new filler/binder for solid dosage forms, and has been recommended as a suitable excipient when a rapidly disintegrating compact is desirable (Kumar et al., 2002; Reus et al., 2004; Reus and Kumar, 2006). However, the main shortcoming of this excipient is its low compactibility and its fibrous shape, which limit its application to formulate poorly compactable and poorly flowing drugs. Traditionally, excipient functionality has been economically accomplished by engineering particles physically. New grades of existing excipients have been created by modifying the fundamental properties of materials, including their morphology, particle size, shape, surface area, porosity and density. These modifications can result in improved derived properties such as flowability, compressibility, compactibility, dilution, disintegration and lubrication potentials (Block et al., 2009; Reimerdes, 1993). However, if one attribute is improved, another could be compromised. For example, Avicel® products have been engineered in different size grades such as Avicel® PH200, which has excellent flow properties but a poor compactibility. Conversely, Avicel® PH101 has poor flow properties, but excellent compactibility (Lerk et al., 1974). One of the most successful approaches used in recent years for particle engineering is coprocessing two or three excipients together. In this technique, excipients interact at the particle level, enhancing functionality as well as masking the undesirable properties of the individual components (Block et al., 2009). The resulting excipient has superior properties compared to the physical blending of the individual components. Excipients that are physically modified in this fashion do not lose their chemical structure and stability, and they maintain their independent chemical properties (Chow et al., 2008). Particles of one material can be incorporated onto the companion material by spray-drying, wet granulation, spheronization, co-milling, co-crystallization, and other techniques.

Amorphous SiO_2 has been widely used as a flow enhancer in powder formulations for food and pharmaceutical applications. Recently, it has been used as a companion excipient for coprocessing with starch (10:1), chitin (1:1), or cellulose I (98:2) resulting in products with improved unique characteristics different from the parent materials (Badwan et al., 2008). For example starch:SiO_2 compacts disintegrate rapidly, often within 30 s. Chitin:SiO_2 powders have increased bulk density and good flow properties (Rashid et al., 2008). Likewise, cellulose I:SiO_2 products have excellent compaction properties, show less sticking to the lower punches and have superior dissolution stability over the physical mixture of MCCI and SiO_2 (Tobyn et al., 1998; Edge et al., 2000; Aljaberi et al., 2009). Further, calorimetric and water sorption studies determined a surface heterogeneity for SMCCI (Qian and Bogner, 2010). For all the above reasons, coprocessing materials are gaining wider acceptance (Moreton, 2000). After conducting preliminary screening studies using several coprocessing companion materials and different techniques, SiO_2 along with spray drying was the only

combination that improved the mechanical properties of MCCII without detriment of its self-disintegrating characteristics. Therefore, the goal of this paper was to present, evaluate and discuss the resulting improved properties of this coprocessed MCCII:SiO$_2$ material. These properties were also compared with commercially available silicified cellulose I materials such as ProSolv® SMCC50 and ProSolv® SMCC90.

2. Materials and methods

2.1. Materials

Cotton linter sheets (grade R270) were obtained from Southern Cellulose Products, Inc. (Chattanooga, TN). Hydrochloric acid and sodium hydroxide were purchased from Fisher Scientific (Fair Lawn, NJ). Magnesium stearate (Powder HyQual®, Lot 2256KXDS) was received from Mallinckrodt Baker (Phillipsburg, NJ). Amorphous SiO$_2$ (Cab-O-Sil® M5, Lot I107) was obtained from Eager Polymers (Chicago, IL). ProSolv® SMCC50 (Lot XCSD9D661X) and ProSolv® SMCC90 (Lot XCSD5B61X) were received from JRS Pharma (Patterson, NY).

2.2. Preparation of microcrystalline cellulose II (MCCII)

Cotton linter strips were soaked in 7.5 N NaOH for 72 h (cellulose:NaOH ratio 1:6, w/v) with periodic stirring at room temperature. The NaOH-treated cotton linter strips were collected by filtration and washed with distilled water until the pH of the washings was between 5 and 7. Approximately 280 g of the dry material was then transferred to a five-liter reactor and 2 L of 1 N HCl was added. The mixture was allowed to stand at room temperature for 1 h and then heated at ∼105 °C. When the linters were reduced to small pieces, the reaction mixture was stirred at 600 rpm. The heating was continued for an additional 1.5–2.0 h. The reaction mixture was then cooled to room temperature and filtered. The white powder obtained was washed with distilled water until the washings reached a pH between 5 and 7. The powder was then dried at room temperature until it passed freely through a US #20 mesh (850 μm) screen and had moisture content (MC) of ∼5%.

2.3. Preparation of silicified microcrystalline cellulose II (SMCCII)

Appropriate amounts of MCCII and SiO$_2$, were mixed to provide a 95:5 w/w ratio, then distilled water was added to obtain a 3% dispersion using a homogenizer (BioSpec Products, Inc., Bartlesville, OK) for 10 min at 10,000 rpm. A Yamato Pulvis® spray-drier (Model GB-22, Yamato Scientific Co., Tokyo, Japan) was employed at the previously optimized conditions of inlet air temperature (IT) 195 °C; atomizing air pressure (AA) 1.0 kg-f/cm^2; drying air rate (DA) 0.44 m^3/min; feed flow rate (FR) 2.0 mL/min and nozzle diameter (ND) 0.7 mm.

2.4. Powder properties and characterization methods

Approximately 100 g of sample was fractionated for 30 min on a Ro-Tap® sieve shaker (Model, RX29, W.S. Tyler Company, Mentor, OH) using stainless steel 600, 420, 250, 177, 150, 125, 105, 75, 53, 45, and 38 μm size sieves, stacked together in the order mentioned. For MCCII the fraction that contained particles between 75 μm and 125 μm corresponding to an average particle size of about 90 μm was used in the study. All other products were used as obtained. Geometric mean diameters (d_g) were determined from the log-normal distribution plot of sieve mean diameters versus cumulative percent frequency using the Minitab statistical software (v.15, Minitab, Inc., State College, PA).

Degree of crystallinity (DC) was obtained on a Siemens powder X-ray diffractometer (Model D5000), using monochromatic CuK (λ_1 = 1.54060 Å, λ_2 = 1.54438 Å) radiation. The Diffrac® Plus software (Eva, version 2.0, Siemens Energy and Automation, Inc., Madison, WI) was used for the data analysis. DC was calculated using the expression: %DC = $100 \times I_C/(I_C + I_a)$, where I_C is the sum of the areas of all diffracted X-ray peaks and I_a is the area of the diffuse halo due to the amorphous region.

A helium displacement micropycnometer (Model MPY-2, Quantachrome Corporation, Boynton Beach, FL) was employed. Samples were dried in a vacuum desiccator (Precision Scientific Co., Chicago, IL) at 60 °C, and at a reduced pressure of 60 μm Hg for 24 h, followed by purging with helium for at least 40 min before each measurement. The true density was calculated by dividing the mass of the material by its volume obtained from the equation:

$$V_p = V_c - V_r \times \left(\frac{P_1}{P_2} - 1 \right) \tag{1}$$

where V_p is the volume of the powder, V_c is the cell volume, V_r is the reference cell volume, P_1 is the pressure in the cell, and P_2 is the pressure outside the cell.

Bulk density (ρ_{bulk}) was obtained directly from the ratio of 20 g powder to its volume measured in a 100 mL graduated cylinder. Tap density (ρ_{tap}) was determined using a VanKel tap density analyzer (Model 50-1000, VanKel Industries, Cary, NC), and measuring the volume after 1200 taps. Porosity (ε) of the powder was determined from the equation:

$$\varepsilon \ (\%) = \left(1 - \frac{\rho_{bulk}}{\rho_{true}} \right) \times 100. \tag{2}$$

Degree of polymerization was obtained from the intrinsic viscosity [η] (ASTM D 1795; USP 28/NF23, 2005) obtained at 25 ± 0.5 °C using an Oswald capillary viscometer (size 50) and cupric ethylenediamine hydroxide (CUEN) as the solvent, according to the relationship:

$$DP = 190 \times [\eta] \tag{3}$$

Loss on drying was obtained using a mechanical convection oven (Model STM 80, Precision Scientific, Inc., Chicago, IL) at 105 °C for 3 h.

Flow rate was measured in a custom made flow meter, which consisted of a stainless steel cylinder (2.5 cm × 20.0 cm), equipped with a steel plate with a circular orifice (19.1 mm). Flowability, expressed as flow rate (g/s) was determined by filling the cylinder with ∼20 g of the powder and measuring flow time through the orifice.

2.5. Morphology of the composite materials

SEM photographs were obtained using a scanning electron microscope (Model S-4800, Hitachi, Hitachi High Technologies America, Inc., and Pleasanton, CA). The powder was fixed on an aluminum stub using double-sided adhesive tape, and coated with a thin layer (3–5 mm) of gold/palladium (60/40) for 4 min on a sputter coater (Model, Emitech K550). The acceleration voltage employed was 5 kV.

2.6. Surface area analysis

It was performed using a Quantasorb surface area analyzer (Quantachrome Corp., Boynton Beach, FL). Helium gas was used as the carrier and diluent gas, while nitrogen gas was used as the adsorbate. A capillary cell (part # 74002) was used for the analysis. Before performing the surface area measurements, samples were dried in a vacuum oven (Model 68351, Precision Scientific Co., Chicago, IL) at 60 °C and at 40 mm Hg for 24 h. Measurements were

conducted at relative pressures (P/P_0) ranging from 0.05 to 0.25 and the specific surface areas were obtained by the BET method (Adamson and Gast, 1997).

2.7. Preparation of tablets

Approximately, 500 mg of powder was compressed on a hydraulic press (Model C, Carver Press, Menomonee Falls, WI) at pressures ranging from 10 to 260 MPa using a flat-faced 13 mm punch and die set at a dwell time of 30 s. The upper punch was equipped with a load cell (Model: LCGD-10K, range 0–10,000 lb, Omega Engineering, Inc., Stamford, CT) and a strain gauge meter (Model: DP25B-S, Omega Engineering, Inc., Stamford, CT). Tablets were kept in a desiccator over Drierite® for 48 h before the analysis.

2.8. Compactibility analysis

A Q-test I universal tester (Model, QT-1, MTS, System Corp., Eden Prairie, MN) was employed to determine the compact tensile strength. Cylindrical compacts were prepared as described in Section 2.7. The force–deflection curves were obtained using the TestWorks® QT software v. 2.03 (MTS Systems Corp., Eden Prairie, MN). The crosshead speed of the upper platen was kept constant at 0.01 mm/s.

The radial tensile strength (TS) values were obtained according to the Fell and Newton equation from the breaking force given by the load–deflection curves (Fell and Newton, 1968):

$$\text{TS} = \left[\frac{2F}{\pi \times D \times t} \right] \tag{4}$$

where F is the breaking force needed to break the compact into two halves, D is the diameter of the compact (mm), and t is the compact thickness (mm). The data of radial tensile strength versus the product of the solid fraction and the compression pressure was fitted according to the Leuenberger model (Lanz, 2005):

$$\text{TS} = T_{max} \times (1 - e^{(-\gamma_c \times P \times \rho_r)}) \tag{5}$$

where TS is the radial tensile strength (MPa), T_{max} is the theoretical tensile strength at infinite compression pressure, γ_c is the compression susceptibility parameter (MPa^{-1}), ρ_r is the compact relative density and P is the compression pressure. Data fitting was performed employing the Statgraphic® software (StatPoint Technologies, Warrenton, VA).

2.9. Compressibility analysis

Compact volume reduction was calculated using the relationship: $V = \pi r^2 h$, where r (mm) is the radius and h is the thickness (mm) of the compact. Compact dimensions (diameter and thickness) were measured with an electronic caliper (Ted Pella Inc., Redding, CA). Compact densification was fitted to the linear and Kawakita models. Heckel proposed a model for powder compressibility, which is given by:

$$\ln\left(\frac{1}{1-D}\right) = kP + A, \quad D = \frac{\rho_a}{\rho_t}, \quad \varepsilon = 1 - D \tag{6}$$

where D is the relative compact density (solid fraction) at pressure P, ε is the porosity of the compact and A the intercept. It represents the powder densification by die filling and particle rearrangement before deformation and bonding of discrete particles take place. The slope of the linear portion of the plot is inversely related to the yield pressure (P_y) or yield stress, which is a measure of the plasticity of the compressed material (Alderborn and Nyström, 1996). The Kawakita model describes the relationship between the degree of volume reduction of the powder and the

applied pressure (Kawakita and Ludde, 1971). The Kawakita model is given by:

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab}, \quad C = 1 - \frac{\rho_0}{\rho_a} \tag{7}$$

where ρ_a, ρ_0, C, and P are the compact apparent density, powder bulk density, degree of volume reduction and compression pressure, respectively. The constant "a" is the compressibility index, which is related to the total volume reduction for the powder bed, and the constant "b" is related to the resistant forces (friction/cohesion) to compression (Hedden et al., 2006).

2.10. Lubricant sensitivity

For the lubricant sensitivity analysis cellulose powders and magnesium stearate (1% w/w) were mixed using a twin shell blender (Model LB429, Patterson-Kelley Co., East Stroudsburg, PA) at times from 5 to 60 min. Compacts of ~500 mg were made at 60 MPa compression pressure as described in Section 2.7. Lubricant sensitivity was expressed as a ratio according to the relationship:

$$\text{LSR} = \frac{S_0 - S_{lub}}{S_0} \tag{8}$$

where S_0 and S_{lub} are the crushing strengths of tablets prepared without and with lubricant, respectively. This test was performed on a Schleuniger Pharmatron 8 M tablet hardness tester (Dr. Scheleuniger Pharmatron Inc., Manchester, NH).

2.11. Brittle fracture index, Young's modulus and toughness

Square compacts of 1.96 cm^2 weighting ~3 g and having a solid fraction between 0.6 and 0.7 were made on a stainless steel split die, die yoke using a hydraulic press system (Model 341-20, Loomis Engineering and Manufacturing Company, Cadwell, NJ) coupled with a motor (Model C6117DB7C, Leeson, Electric Corporation, Grafton, WI) and a pump (Model F051, Brand Hydraulics, Omaha, NE). This system allows for uniaxial compression and triaxial decompression, minimizing capping. The compression velocity used was 2 mm/s, a dwell time of 30 s and decompression time of 1 s. In addition, square compromised compacts were made with an 1 mm hole diameter in the center. Compacts were stored in a desiccator between 15 and 30% RH for 48 h and the resulting stress–strain curves were obtained on a universal stress–strain analyzer (Model Q-test I, Material Testing Systems, Cary, NC). Since the rate force approximates to an exponential curve, the selected crosshead rate was adjusted such that the time between 1/e of maximum force was ~15 s (Hiestand et al., 2006). The Young's modulus was obtained from the slope of the stress–strain curves. It measures the stiffness (resistance of an elastic body to an applied force) of a given material. The toughness of the material was obtained by measuring the area under the curve of the resulting stress–strain curves. The brittle fracture index (BFI) was calculated from the Hiestand equation:

$$\text{BFI} = 0.5 \left[\left\lfloor \frac{\sigma}{\sigma_0} \right\rfloor - 1 \right] \tag{9}$$

where σ is the tensile strength of normal compacts and σ_0 is the tensile strength of the compromised compacts.

2.12. Disintegration studies

Disintegration tests were performed in distilled water according to the USP specifications, employing an Erweka GmbH disintegration apparatus (type 712, Erweka, Offenbach, Germany) (United States Pharmacopoeial Convention, 2005).

2.13. Griseofulvin release studies

Since a fast disintegrating vehicle is desirable to formulate poorly soluble drugs, griseofulvin (solubility of 0.0346 mM) was used as a model drug to challenge the release properties from the excipients studied (Zilia et al., 2005). Compacts were made by mixing 125 mg of griseofulvin and 375 mg of excipient with a mortar and pestle for 10 min followed by compression as described in Section 2.7. The USP 25 dissolution method was employed (United States Pharmacopoeial Convention, 2005). Aliquots were diluted in a methanol:water (4:1) solvent and analyzed by UV–vis spectrophotometry (Hewlett Packard, Model 8453, Isco, Inc., Lincoln, NE). The dissolution study was performed using the USP Apparatus 2 (Pharma Test, Scientific Instruments and Technology Corp., Piscataway, NJ) at 75 rpm for 90 min in a medium containing 40 mg/mL of sodium lauryl sulfate. The absorbance was measured at 291 nm on the filtered aliquots of the dissolution medium.

2.14. Reprocessing susceptibility

A classic poorly compactable drug such acetaminophen was selected to test the reprocessing susceptibility of the materials (Martinello et al., 2006). Approximately, 25 g of an acetaminophen:excipient (50:50) mixture was prepared using a V-blender for 30 min. Round compacts of about 1 g of the mixture were made in the hydraulic Loomis press using a 13 mm round flat faced tooling at a dwell time of 30 s. Compacts were analyzed for tensile strength on a Q-test machine (Model Q-test I, Material Testing Systems, Cary, NC) and then milled using a roller mill (Model KU 1, Erweka GmbH, Chemical and Pharmaceutical Industry, New York, NY). The milled samples were passed freely on a 140-mesh sieve and compressed again under the same conditions, and the resulting tensile strength was determined.

2.15. Statistics

The one-way ANOVA analysis was conducted for each test at a significance level of 0.05. All tests were performed in replicates of three independent samples.

3. Results and discussion

3.1. Powder properties

Table 1 shows the powder properties of MCCII and SMCCII in comparison to commercial products. The true density of all samples was comparable and their moisture content ranged from 3 to 4%, which was well below the USP limit of 7%. Silicified cellulose I samples such as ProSolv® SMCC50 and ProSolv® SMCC90 had lower bulk and tap densities than MCCII and SMCCII. In fact, SMCCII presented higher bulk and tap densities than MCCII. This phenomenon is due to the lower particle size and higher consolidation achieved by the production process, which involved spray drying (Fig. 1). Thus, SMCCII presented a more regular, smooth and semispherical particles, which were more compactable than MCCII. Conversely, the non-processed MCCII consisted of loose fibrous particles, which did not pack well and hence had large bulk and tap densities. SMCCII and ProSolv® SMCC samples had more morphological features than MCCII. This means, they had rough surfaces due to the SiO_2 clusters, as well as protrusions and cavities, which might contribute to their packing tendency. All materials presented a high porosity (>0.76) except for SMCCII. In this case, the semispherical shape of the particles and the lack of rough features made this sample pack more readily, and hence its porosity was reduced. The degree of polymerization of MCCII (79) and SMCCII (95) was lower than those of commercial SMCCI (192–206). It has been reported that

the degree of polymerization of cellulose II is always lower than that of cellulose I (Krassig, 1996). The specific surface area obtained by the BET analysis showed that silicified samples such as SMCCII, ProSolv® SMCC50 and ProSolv® SMCC90 had larger surface areas than the non-silicified MCCII. The presence of SiO_2 nanoparticles on the surface increased the total surface area compared to the corresponding non-silicified materials (Steele et al., 2004). SMCCII had the largest surface area because it contained the largest concentration of SiO_2 (5%). As a result, SMCCII samples had surface areas of about 20 times larger than MCCII. It has been reported that ProSolv® SMCC samples had surface areas about four times larger than Avicel® products (Steele et al., 2004). No major differences were observed between the degree of crystallinity of silicified and non-silicified samples except for SMCCII, whose degree of crystallinity was slightly lower, probably due to the high content of amorphous SiO_2, which tended to reduce the apparent crystallinity of the cellulose. Three levels of particle size expressed as geometric means were observed, the largest was observed in MCCII, the intermediate level was observed in ProSolv® SMCC90 and the smallest was observed in SMCCII and ProSolv® SMCC50. In this case, the spray drying process in SMCCII played a major role in reducing the particle size and in changing the original fibrous morphology. The flow rate of the samples ranged in the increasing order as: MCCII < ProSolv® SMCC50 < SMCCII < ProSolv® SMCC90. SMCCII exhibited a flow rate two-fold higher than that of MCCII due to its high densification, more regular morphology and reduced porosity. It has been reported that ProSolv® SMCC materials have slightly higher flowability than plain MCCI samples (Lahdenpaa et al., 2001).

3.2. Tableting properties

3.2.1. Mechanical properties (tensile strength, BFI, toughness and Young's modulus)

The parameters derived from the Leuenberger model for tensile strength are shown in Table 2. The compression susceptibility (γ_c) values were large (0.005–0.006 MPa^{-1}) for highly plastic deforming materials such as ProSolv® SMCC50 and ProSolv® SMCC90. In contrast, cellulose II materials such as MCCII and SMCCII exhibited the lowest γ_c values (0.002–0.003 MPa^{-1}). Except for MCCII, most materials exhibited a high T_{max}. Further, since the curves of ProSolv® SMCC50 and ProSolv® SMCC90 reached a plateau faster with increasing compression pressure than SMCCII, the predicted maximum tensile strength values (T_{max}) for these products were lower (20.7–21.6 MPa). Further, SMCCII had a higher tensile strength and hence, better compactibility than MCCII. Thus, SMCCII had a T_{max} four times larger than that of MCCII.

Likewise, compactibility expressed as the area under the tensile strength (AUCTS) of SMCCII, was about 2.5 times larger than that of MCCII. Conversely, ProSolv® SMCC samples had an AUCTS about 3.4 times larger than MCCII.

The brittle fracture index (BFI) is a measure of the ability of a compact to relieve stress that is caused by the presence of a defective region (hole) in a tablet. The presence of this hole in the center creates a stress concentration factor which can be found by:

$$f = 1 + 2\sqrt{\left[\frac{L}{R}\right]} = 3 \tag{10}$$

where L is half the length of the hole (0.5 mm), and R is the radius of the curvature of the tip of the hole (0.5 mm). This means that tension fracture is expected to occur at 1/3 of the tensile strength when the hole is present and the compact cannot relieve the stress at the edge of the hole by plastic deformation (Hiestand and Smith, 1984). For example, when the ratio of the compromised and uncompromised tensile strength (σ_T/σ_{T_0}) in the BFI (Eq. (9)) is 3, the resulting BFI is 1, indicating that the material cannot relieve stress by plastic

Table 1
Powder properties of MCCII, SMCCII and commercial products.

Material	True density (g/cm³) (n = 3)	Loss on drying (%) (n = 1)	Bulk density (g/cm³) (n = 3)	Tap density (g/cm³) (n = 3)	Powder porosity (n = 3)
MCCII	1.54 (0.02)	3.1	0.38 (0.03)	0.54 (0.06)	0.76
SMCCII	1.57 (0.00)	3.1	0.45 (0.00)	0.69 (0.03)	0.70
ProSolv® SMCC50	1.56 (0.01)	3.0	0.32 (0.00)	0.44 (0.01)	0.79
ProSolv® SMCC90	1.55 (0.00)	3.3	0.28 (0.00)	0.36 (0.00)	0.82
SiO₂	2.27 (0.01)	1.5	0.04 (0.00)	0.08 (0.00)	0.98
p-Value (α = 0.05)	0.052	N.A.	0.00	0.00	N.A.

Material	Degree of polymerization (n = 5)	SSA$_{BET}$ (m²/g) (n = 3)	Degree of crystallinity (%) (n = 3)	Geometric mean diameter (μm) (n = 3)	Flow rate (g/s) (19.1 mm) (n = 3)
MCCII	79 (5)	0.5 (0.1)	68 (1)	258 (42)	3.3 (0.1)
SMCCII	95 (5)	10.5 (0.1)	62 (4)	64 (9)	6.7 (1.0)
ProSolv® SMCC50	192 (6)	6.3 (0.0)	68 (2)	58 (5)	5.5 (0.6)
ProSolv® SMCC90	206 (4)	5.5 (0.0)	67 (2)	110 (9)	9.5 (0.2)
SiO₂	N.A.	196.2 (1.5)	0 (0)	15 (4)	0 (0)
p-Value (α = 0.05)	0.000	0.00	0.053	0.00	0.00

N.A., not applicable.

deformation, but by brittleness. In contrast, when σ_T/σ_{T_0} is 1, the resulting BFI is 0 and the stress relief is accomplished only by plastic deformation. The BFI obtained from the square compacts (Table 2) exhibits two trends in the values. The lowest BFI is observed for ProSolv® SMCC samples (0.02–0.04); and the highest values are observed for MCCII and for SMCCII (0.22–0.27). Hiestand and Smith found a BFI for Avicel® PH102 of from 0.04 to 0.09, and Williams and collaborators found a BFI for Avicel® PH101 of from 0.03 to 0.08, and they concluded that variations in the BFI were due to the lot type (Hiestand and Smith, 1984; Williams et al., 1997). The differences between our results and Hiestand's could also be due to the solid fraction range employed. Hiestand used a range from 0.8 to 0.9 and we employed a range from 0.6 to 0.7 because of the high

values of tensile strength produced at solid fractions >0.8. These exceeded the maximum tolerable limit of the equipment. MCCII and SMCCII *per se* had a more brittle character than Prosolv® SMCC50 and Prosolv® SMCC90. For example, SMCCII had a higher BFI than MCCII indicating that the presence of 5% SiO₂ causes an increase in the brittle behavior of the material. Although there are no reports of the BFI for Prosolv®, our results fall within the range reported by Hiestand for MCCI (Avicel® products).

The toughness of the materials was calculated from the area under the curve of the stress–strain curves obtained from the square compacts. Toughness is the resistance of a material when compressed until breaking (Alderborn and Nyström, 1996; Hancock et al., 2000). Except for SMCCII, all cellulosic materials can
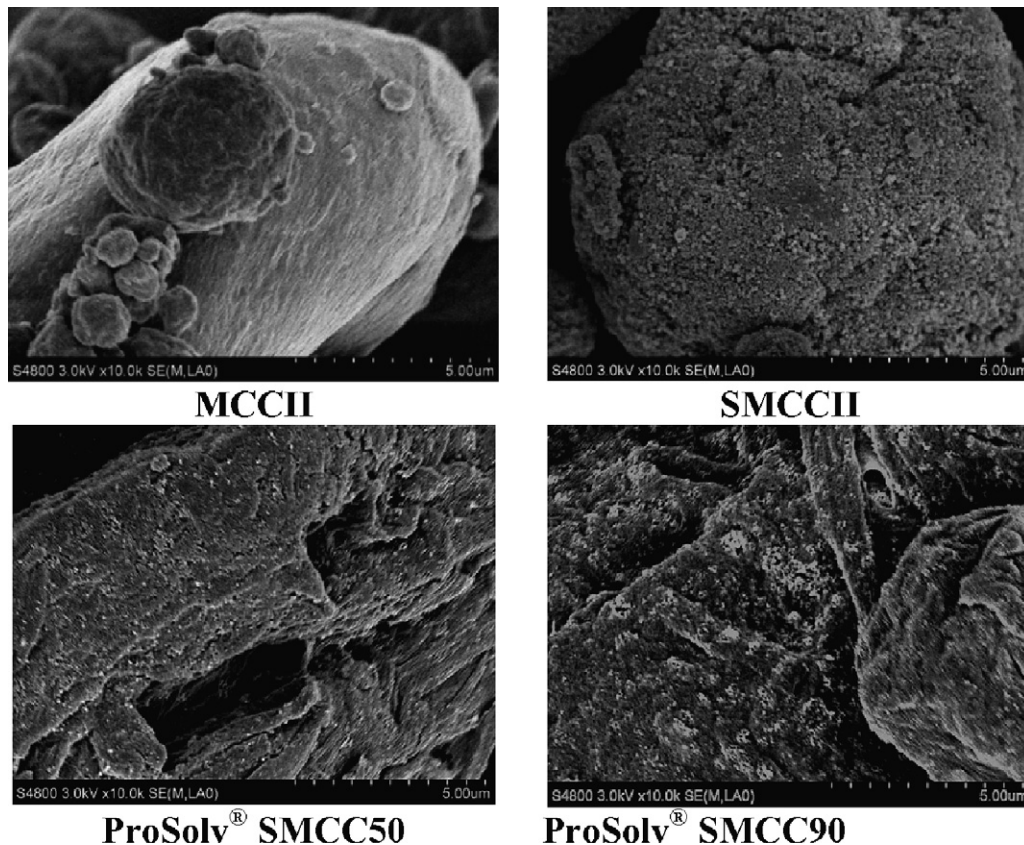

Fig. 1. SEM pictures of MCCII, SMCCII and commercial products.

Table 2
Parameters derived from the Leuenberger Model, BFI and Young's modulus.

Sample	Leuenberger model				Mechanical properties of the square compacts				
	AUCTS (MPa^2)[a]	T_{max} (MPa)[b]	γ_c (MPa^{-1})[c]	R^2	BFI[d]	E' (GPa)[e]	Max. stress (MPa)[f]	Max. strain (%)[g]	T (MPa)[h]
MCCII	680.5	9.9	0.003	0.9835	0.22 (0.00)	0.25 (0.07)	3.30 (0.25)	1.47 (0.13)	386 (96)
SMCCII	1683.2	40.0	0.002	0.9960	0.27 (0.03)	0.31 (0.05)	4.37 (0.19)	1.73 (0.13)	847 (13)
ProSolv® SMCC50	2348.7	20.7	0.006	0.9939	0.04 (0.01)	0.27 (0.00)	3.91 (0.19)	1.68 (0.03)	773 (45)
ProSolv® SMCC 90	2229.8	21.6	0.005	0.9986	0.02 (0.00)	0.25 (0.00)	3.71 (0.02)	1.68 (0.02)	777 (49)
p-Value ($\alpha = 0.05$)	N.A.	N.A.	N.A.	N.A.	0.00	0.38	0.00	0.04	0.00

N.A., not applicable.
[a] Area under the curve of the tensile strength.
[b] Tensile strength at infinite pressure.
[c] Compression susceptibility.
[d] Brittle fracture index.
[e] Young's modulus.
[f] Maximum stress.
[g] Maximum strain.
[h] Toughness.

withstand a minimum of 3 MPa of compression pressure before breaking. The presence of SiO$_2$ on the surface of ProSolv® SMCC50, ProSolv® SMCC90 and SMCCII reinforced their mechanical properties and this was also reflected in their large toughness values. These large values may indicate an increased ability to absorb and withstand the applied energy (Hancock et al., 2000).

The Young's modulus (E') measures the resistance of a material to elastic deformation when a powder is compressed. SMCCII had a higher Young modulus than MCCII, indicating a high resistance to compression. The presence of SiO$_2$ in SMCCII allows for the formation of more binding sites in the particles, resulting in a better compaction and hence, improved mechanical properties during compression. Although there was not a significant difference among the E', MCCII presented the lowest maximum stress, maximum strain values and toughness as obtained from the stress–strain curves. Conversely, SMCCII, ProSolv® SMCC50, and ProSolv® SMCC90 showed comparable values.

3.3. Heckel analysis

Table 3 lists the Heckel parameters of the products evaluated. The yield pressure value (P_y), which is the inverse of the slope of the linear portion of the Heckel curve, refers to the pressure at which the material begins to deform plastically. Compared to cellulose I commercial products, MCCII and SMCCII showed higher P_y values, suggesting that these materials are more brittle. In fact, the presence of SiO$_2$ in SMCCII increased the brittle behavior upon consolidation. Further, cellulose I materials are known to deform by a plastic mechanism, especially if their P_y is lower than 100 MPa (York, 1992). MCCII had lower D_0 values than SMCCII indicating that the presence of SiO$_2$ along with the spray drying process increased the initial packing ability of the materials by die filling. These results are in agreement with the trends observed for the bulk and tap densities, and can be explained by the morphology of MCCII, which was fibrous and smooth, and by the regular morphology of SMCCII. The D_b parameter represents the extent of powder bed arrangement due to particle fragmentation/rearrangement at low pressures, respectively. The fibrous shape of MCCII seems to have a large effect on D_b since this material had the largest D_b suggesting that these fibers are able to accommodate, bend or fragmentate extensively, filling up the interparticular voids in the powder bed at low pressures. Thus, MCCII, which is composed of fibrous particles, is more prone to rearrangement, and consequently, good packing at low applied pressures. Further, SMCCII also gave high D_b values, probably due to the SiO$_2$ aggregates, which cover the cellulose particles. Once the compression starts SiO$_2$ particles move and accommodate between and within the

cellulose particles and their aggregates break down into smaller particles. The rearranging behavior indicated by the D_b of the materials was more evident than packing by die filling (given by the D_0 value).

3.4. Kawakita analysis

The Kawakita parameters of the products are shown in Table 4. The "a" compressibility index was close to the values of powder porosity obtained, and they were inversely related to the bulk and tap densities. For example, SMCCII and ProSolv® SMCC90, exhibited a bulk density of 0.45 and 0.28 g/cm^3, respectively and a tap density of 0.69 and 0.36, respectively. The corresponding compressibility indices ("a" values) were 0.70 and 0.83, respectively, and the porosity values were 0.70 and 0.82, respectively. SMCCII was the least compressible material due to its high bulk and tap densities, low porosity, a more regular and smoother surface, and its low propensity for packing. All other materials had higher "a" values (0.76–0.83). The "b" parameter obtained from the Kawakita analysis is indicative of cohesion between particles. The "b" values indicate that MCCII was the material that exhibited the largest degree of forces opposing to compression, possibly due to the mechanical interlocking and intertwining of fibers. On the other hand, all other materials exhibited relatively low "b" values (from 0.14 to 0.18), indicating that cohesive forces of the powder might play a minor role during compression. Zhang et al. (2002) reported "a" values of 0.71 and 0.80, and b values of 0.08 and 0.13 for ProSolv® SMCC90 and ProSolv® SMCC50, respectively.

SMCCII exhibited high ejection forces probably due to its smaller particle size and high SiO$_2$ content, which might result in an increase in punch and die friction. Thus, it is advantageous during compaction to add magnesium stearate to this product. In contrast, ProSolv® SMCC50 and ProSolv® SMCC90 exhibited the lowest ejection forces (0.05 kN and 0.10 kN, respectively). These two opposite results can be explained by the degree of deformation upon consolidation of MCCI, which exhibits a more plastic deforming mechanism than MCCII. This indicates that fewer fragmenting particles will be formed, and these do not contribute in a great magnitude to friction. On the other hand, SMCCII contained a larger amount of the fragmenting SiO$_2$ and contributed significantly to powder and tooling friction.

3.5. Sensitivity to magnesium stearate

Lubricant sensitivity was tested against magnesium stearate at the 1% level. Magnesium stearate is commonly used in tablet formulations to reduce friction between the material and tooling used. As seen in Fig. 2, the trend for lubricant sensitivity ranged as:

Table 3
Heckel parameters of MCCII, SMCCII and commercial products.

Product	Pressure range (MPa)	Heckel parameters					
		P_y [a]	A [b]	D_0 [c]	D_a [d]	D_b [e]	R^2
MCCII	90–175	115	1.68	0.24	0.81	0.57	0.9880
SMCCII	65–175	150	1.03	0.29	0.64	0.37	0.9940
ProSolv® SMCC50	35–125	98	0.74	0.21	0.52	0.31	0.9976
ProSolv® SMCC90	90–175	108	0.74	0.18	0.52	0.34	0.9949

[a] Powder yield pressure.
[b] Powder total densification.
[c] Relative density due to die filling.
[d] Total powder relative density.
[e] Relative density due to particle rearrangement/fragmentation.

MCCII≅Prosolv® SMCC50 > Prosolv® SMCC90 > SMCCII. In this case, silicification in MCCII increase the brittle character of the material, but at the same time gave a protective effect towards lubricant sensitivity. For instance, MCCII was more sensitive to magnesium stearate than SMCCII and these materials had P_y values of 115 and 150 MPa, respectively.

These results suggest that materials with low P_y values such as MCCII, Prosolv® SMCC50 and Prosolv® SMCC90 are more sensitive to magnesium stearate, and thus, sensitivity decreased as the ductility of the material decreased. Thus, SMCCII had the highest P_y value (150 MPa) and hence, had the lowest lubricant sensitivity.

The low sensitivity to magnesium stearate exhibited by SMCCII is due to the coating effect of SiO_2, which competes with magnesium stearate upon compression to cover the cellulose surface. Thus, the fragmenting behavior of SMCCII creates more new clean surfaces available for binding. Consequently, this fragmenting material possessed less lubricant sensitivity than the more plastically deforming materials. Further, ProSolv® SMCC90 (P_y of 108 MPa) was more fragmenting than ProSolv® SMCC50 (P_y of 98 MPa) and hence, it was less susceptible to magnesium stearate.

Fig. 3 shows the relationship between blending time and lubricant sensitivity. Silicified materials such as SMCCII, ProSolv® SMCC50 and ProSolv® SMCC90 which had a high brittle component,

Table 4
Kawakita parameters of MCCII, SMCCII and commercial products.

Material	Ejection force (kN)	Kawakita parameters		
	(n = 3)	a [a]	b [b]	R^2
MCCII	0.24 (0.02)	0.76	0.31	1.0000
SMCCII	0.46 (0.03)	0.70	0.14	0.9999
ProSolv® SMCC50	0.05 (0.01)	0.78	0.15	1.0000
ProSolv® SMCC90	0.10 (0.02)	0.83	0.18	1.0000
p-Value (α = 0.05)	0.00	N.A.	N.A.	N.A.

N.A., not applicable.
[a] Compressibility index.
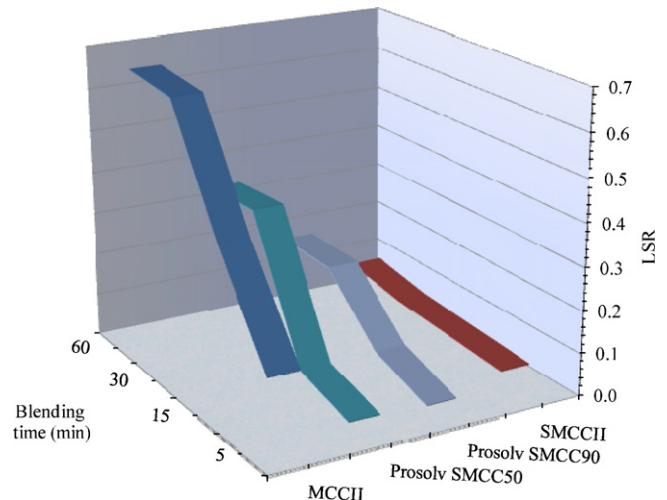[b] Degree of forces which opposed to flow.

Fig. 3. Effect of blending time and lubricant sensitivity of MCCII, SMCCII and commercial samples.

exhibited a lower lubricant sensitivity than MCCII. Furthermore, a plateau in sensitivity is achieved within 30 min of blending for all the materials studied. This suggests that the covering effect of magnesium stearate reaches a limit at 30 min and new available sites for particle binding are formed afterwards. Long mixing times with the lubricant (i.e. 30 min.) had a major effect on lubricant sensitivity for MCCII.

3.6. Disintegration studies

Fig. 4 shows that tablets prepared using MCCII and SMCCII had the fastest disintegration time (maximum 110 s) independent of the compression pressure used. On the other hand, compacts
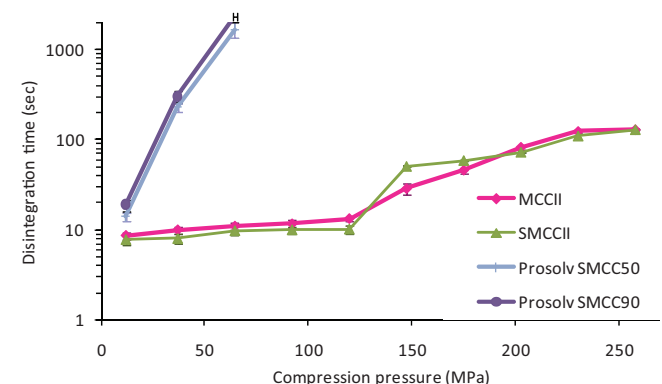

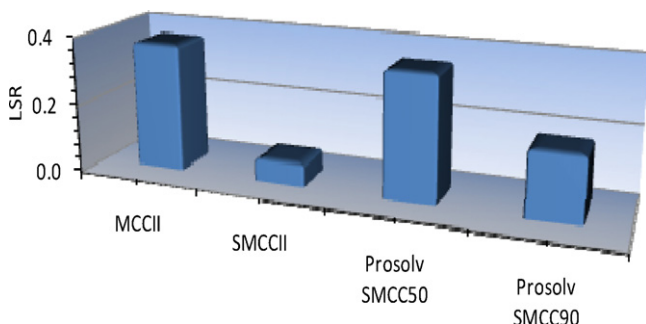**Fig. 2.** Lubricant sensitivity of MCCII, SMCCII and commercial products.

Fig. 4. Compact disintegration of MCCII, SMCCII and commercial products.
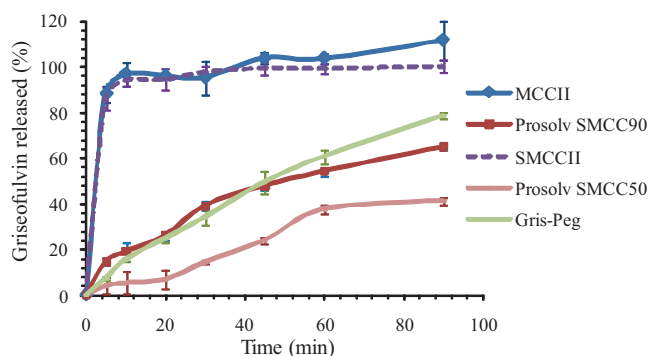
Fig. 5. Griseofulvin dissolution studies of the MCCII, SMCCII and commercial compacts.

made of SMCCI materials exhibited high disintegration values (30–50 min) up to a 60 MPa of compression pressure. Further, SMCCI compacts made at higher compression pressures did not disintegrate during the test period (∼5 h). These results are not surprising since these materials are highly compactable and were able to form strong compacts.

3.7. Dissolution studies

Fig. 5 shows the griseofulvin release profiles of compacts made of the materials studied. MCCII and SMCCII released more than 85% of griseofulvin within 10 min and had the fastest release properties. In contrast, Prosolv® SMCC50 and Prosolv® SMCC90 and the commercial product Gris-Peg® released less than 20% of the API within 10 min. Gris-Peg®, barely fulfilled the 75% release requirement specified in the USP for the 90 min of the test. ProSolv® SMCC50 and ProSolv® SMCC90 due to the formation of strong compacts did not pass the test, suggesting that a disintegrant should be added when these MCCI excipients are employed.

3.8. Reprocessing effects and reworkability

Fig. 6 shows the tensile strength of compacts made of excipient–acetaminophen mixtures before and after reprocessing or double compression. In order to assess the effect of reprocessing, the ANOVA test was conducted. In general, reprocessing and sample type had a negative impact on the tensile strength of the compacts as seen in the ANOVA table ($p = 0.00$; Table 5). In general, the binding ability of the materials is partially lost after the first compaction and hence, compacts after the second compression cycle were weaker. It has been reported that the loss of compactibility is due to the increase in yield pressure. In other words, materials become less plastic after the first compression and further milling (Kochhar,
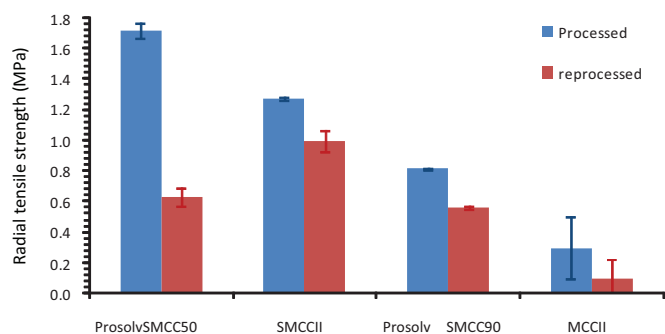

Fig. 6. Reprocessing susceptibility of compacts made of acetaminophen and cellulosic excipients.

Table 5
ANOVA table of the tensile strength of the processed versus reprocessed materials.

Sample	Process	Reprocessed	$\alpha = 0.05$
MCCII	0.3 (0.02)	0.09 (0.02)	0.00
SMCCII	1.27 (0.20)	1.00 (0.13)	0.06
ProSolv® SMCC50	1.72 (0.05)	0.63 (0.06)	0.00
ProSolv® SMCC90	0.81 (0.07)	0.56 (0.05)	0.00
$\alpha = 0.05$	0.00	0.00	

1994). The loss of compactibility was more pronounced for SMCCI materials than for MCCII and SMCCII. Tensile strength of compacts made from the acetaminophen–excipient mixtures ranged as: ProSolv® SMCC50 > SMCCII > ProSolv® SMCC90 > MCCII. ProSolv® SMCC90 seems to be less affected by reprocessing than ProSolv® SMCC50. This phenomenon could be due to the smaller particle size and greater surface area of ProSolv® SMCC50, which might result in increased particle binding and hence, compact formation. After recompression the values of compact tensile strength of ProSolv® SMCC50 and ProSolv® SMCC90 were comparable. In this case, particle size had no effect on compactibility since all samples were passed through a 140-mesh sieve before recompression took place. Studies have suggested that both the work of hardening and a larger particle size, generated after dry granulation, might result in loss of compactibility (Herting and Kleinebudde, 2008). However, in this case dry granulation was not used, but precompression. This could produce similar effects to those produced by dry granulation. The tensile strength of SMCCII compacts was virtually not affected by reprocessing ($p = 0.06$). This might be due to a better distribution and competing effect of SiO_2 and acetaminophen in the powder bed, so SiO_2 take over acetaminophen particles and thus, binding of cellulose particles is not hindered by acetaminophen.

Reworkability refers to the capacity of a material to withstand reprocessing without losing its compactibility (as reflected in the tensile strength). This means that a material with a low loss of recompactibility will have a high workability. If the loss of tensile strength after reprocessing is expressed as a percentage, two trends can be observed. The first trend observed was formed by MCCII and ProSolv® SMCC50 which had a loss of tensile strength from 60 to 70%. The second trend was formed by SMCCII and ProSolv® SMCC90, which showed a minor change in tensile strength after reprocessing. One theory suggests that the loss of reworkability is due to "work hardening". According to this theory, during compression or roller compaction a great number of defects are formed and entanglement of new dislocations occurs in the particles that are being deformed plastically. These defects harden particles and make plastic deformation more difficult on subsequent compactions (Sun and Himmelspach, 2005; He et al., 2007). The overall trend for workability ranged as: SMCCII > ProSolv® SMCC90 > ProSolv® SMCC50 > MCCII.

4. Conclusions

The novel silicified microcrystalline cellulose (SMCCII) was created to enhance the functional properties of microcrystalline cellulose II (MCCII). SMCCII provided more benefits in terms of functionality as compared with MCCII, than those provided by ProSolv® SMCC products. SMCCII had a high bulk and tap densities, high packing tendency, reduced porosity, high surface area, and high flow rates compared with MCCII. SMCCII presented the highest brittleness among all materials because of its high SiO_2 content. Its toughness and Young's modulus were comparable to those of commercial products. SMCCII was the least sensitive material to magnesium stearate and its compactibility was not affected by blending time. Griseofulvin tablets prepared using this excipient exhibited a rapid release time, and its compacts made with

acetaminophen showed the greatest reworkability. This new excipient has a potential for use in direct compression applications.

Acknowledgments

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