

## Effect of Silicification on the Tableting Performance of Cellulose II: A Novel Multifunctional Excipient

John Rojas\*<sup>a</sup> and Vijay Kumar<sup>b</sup>

<sup>a</sup>Department of Pharmacy, School of Pharmaceutical Chemistry, The University of Antioquia; Medellín 094, Colombia; and <sup>b</sup>Division of Pharmaceutics and Translational Therapeutics, College of Pharmacy, The University of Iowa; Iowa City, IA 52242, U.S.A.

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The effect of silicification on the tableting performance of microcrystalline cellulose II (MCCII) was assessed through coprocessing with fumed silica *via* spray drying and wet granulation at the 98:2, 95:5, 90:10 and 80:20 ratios. Compacts produced by spray drying and wet granulation rendered better tensile strength than MCCII. The Kawakita and Heckel models implied that silicification increased compressibility and decreased the plastic deforming behavior and densification by die filling at the early stage of compression for MCCII. It also decreased the sensitivity to hydrophobic lubricants such as magnesium stearate, especially for the spray-dried products due to the competing effect with magnesium stearate. Further, silicification decreased the high elastic recovery typical of MCCII due to the increase in specific surface area and fragmenting behavior which contributed to the formation of stronger compacts. Moreover, silicification did not affect the fast disintegrating properties and release rates of poorly soluble drugs such as griseofulvin formulated in tablets compared to those of Prosolv<sup>®</sup> SMCC 50 and Prosolv<sup>®</sup> SMCC 90. The new silicified materials are appropriate to formulate fast disintegrating tablets by direct compression.

**Key words** coprocessed excipient; direct compression; fumed silica; microcrystalline cellulose II

Ideally, during a formulation process a combination of a plastic and brittle material is necessary for optimum tableting performance.<sup>1)</sup> This combination prevents the storage of too much elastic energy during powder compression, which is associated to the formation of weak compacts and the tendency for capping and lamination.<sup>2)</sup> Further, excipients with one of these two types of deformation can be coprocessed to produce a synergistic effect by selectively overcoming the disadvantages of the individual components. Such combinations can help improving functionalities such as compaction performance, compressibility and sensitivity to moisture. The products so formed are physically modified in a way that they do not lose their chemical structure and stability. In other words, excipients maintain their independent chemical properties; while, synergistically increase their functional performance.<sup>3)</sup> Typically, coprocessed materials exhibit superior properties than the parent individual components. The randomized embedding of the components in the particles minimizes their anisotropic behavior. So, deformation can occur along any plane and multiple clean surfaces are formed during the compaction process.<sup>4)</sup> A major limitation of a coprocessed excipient is that the ratio of the components in a mixture is fixed and in developing a new formulation, a fixed ratio of the excipients may not be an optimum choice for the drug at the dose per tablet under development.<sup>5,6)</sup>

Microcrystalline cellulose II (MCCII), a new allomorph of cellulose was recently introduced as a new multifunctional excipient, especially due to its great ability to uptake water independent of the processing employed. For this reason, this excipient is ideal to formulate rapidly disintegrating compacts compared to other cellulosic excipients.<sup>7,8)</sup> Processing such as spray drying and wet granulation improved compactibility, dilution potential, flow and powder density due to the transformation of a fiber morphology to a more regularly-shaped particle without changing the apparent plastic deformation mechanism under consolidation.<sup>9)</sup> Since MCCII shows lower

mechanical properties compared to microcrystalline cellulose I, it is an ideal candidate for coprocessing with a more brittle deforming material having a high surface area such as fumed silica (200 m<sup>2</sup>/g). Therefore, in a previous study, coprocessing of MCCII with fumed silica at the 98:2, 95:5, 90:10 and 80:20 ratios by spray drying, wet granulation and spheronization was conducted and the particle properties were evaluated.<sup>10,11)</sup> They found spheronization followed by wet granulated and spray dried products to have the highest particle size, flow, tap density, but the lowest porosity and Hausner ratio independent of silicification level. On the contrary, properties such as true density, specific surface area and degree of crystallinity were more silicification dependent rather than processing dependent. Conversely, the degree of polymerization and moisture content were silicification and processing independent, whereas, sorption and swelling decreased only at the 20% silicification level independent of the process employed. However, the effect of fumed silica in tableting was not deeply assessed. For this reason, the goal of this study is to evaluate mechanistically the effect of fumed silica on the tableting performance of MCCII and to explore the possible direct compression applications of these silicified materials.

### Experimental

**Materials** Cotton linter sheets (grade R270) were obtained from Southern Cellulose Products, Inc. (Chattanooga, TN, U.S.A.). Hydrochloric acid and sodium hydroxide were purchased from Fisher Scientific (Fair Lawn, NJ, U.S.A.). Magnesium stearate (Powder Hyqual<sup>®</sup>, Lot 2256KXDS) was received from Mallinckrodt Baker (Phillipsburg, NJ, U.S.A.). Amorphous silicon dioxide (Cab-o-Sil M5, lot I107) was obtained from Eager polymers (Chicago, IL, U.S.A.). Prosolv<sup>®</sup> SMCC50 (lot XCSD9D661X) and Prosolv<sup>®</sup> SMCC90 (lot XCSD5B61X) were received from JRS Pharma (Patterson, NY, U.S.A.).

**Methods. Preparation of Cellulose II Powder (MCCII)**

\* To whom correspondence should be addressed. e-mail: jrojasca@gmail.com

Cotton linter was soaked in 7.5N NaOH for 72h (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 pH ranging between 5 and 7. Approximately 280g of the dry material was then transferred to a five-liter reactor and 2L of 1N HCl was added. The mixture was allowed to stand at room temperature for one hour and then heated at *ca.* 105°C. When the linters were reduced to small pieces, the reaction mixture was stirred at 600rpm. The heating was continued for an additional 1.5–2.0h. The reaction mixture was then cooled to room temperature and filtered. The white powder obtained was washed with distilled water until reaching a pH between 5 and 7 and then dried at room temperature until passed freely through a #20 mesh (850 $\mu$ m) screen and contained a moisture content (MC) of *ca.* 5%.

#### Preparation of CII-SiO<sub>2</sub> Composites by Spray Drying

Appropriate amounts of MCCII slurry and SiO<sub>2</sub>, equivalent to give 98:2, 95:5, 90:10, and 80:20 w/w ratios, were mixed and diluted with distilled water to obtain a 3% dispersion using a homogenizer (Biospec products, Inc., Bartlesville, OK, U.S.A.) for 10min at 10000rpm. A Yamato Pulvis spray-drier (Model GB-22, Yamato Scientific, Co., Tokyo, Japan) was employed at the previously optimized spraying conditions of inlet air temperature (IT), 195°C; atomization air pressure (AA), 1.0kg-f/cm<sup>2</sup>; drying air speed (DA), 0.44m<sup>3</sup>/min; feed flow rate (FR), 2.0mL/min and nozzle diameter (ND), 0.7mm.<sup>8)</sup>

#### Preparation of CII-SiO<sub>2</sub> Composites by Wet Granulation

Appropriate amounts of MCCII slurry and SiO<sub>2</sub>, equivalent to give 98:2, 95:5, 90:10, and 80:20 w/w ratios, were mixed and diluted with distilled water to obtain a 5% dispersion using a homogenizer (Biospec products, Inc., Bartlesville, OK, U.S.A.) for 10min at 10000rpm at room temperature. The resulting homogeneous mixture was collected by vacuum filtration and sequentially granulated on an Erweka oscillating granulator (Model AR400, Chemical and Pharmaceutical Industry, Inc., New York, NY, U.S.A.) using a 710 $\mu$ m, 250 $\mu$ m and 150 $\mu$ m aperture screen size when the moisture content was *ca.* 45, 30 and 20%, respectively. The granules obtained were dried, either in air or in a convection oven at 35°C until the moisture content was less than 5%.

**Morphology of the Silicified Materials** Scanning electron microscope (SEM) photographs were obtained using a scanning electron microscope (Model S-4800, Hitachi, Hitachi High Technologies America, Inc., Pleasanton, CA, U.S.A.). Powders were fixed on an aluminum stub using a double sided adhesive tape and coated using a sputter coater (Model, Emitech K550). Samples were sputtered with a thin layer (3–5 nm) of gold/palladium (60:40) under an argon atmosphere for four minutes at 30W. The acceleration voltage employed was 5kV.

**Specific Surface Area** These measurements were performed using a Quantasorb sorption system (Quantachrome Corp., Boynton Beach, FL, U.S.A.). Helium was used as the carrier and diluent gas, while nitrogen gas was used as the adsorbate. Before performing the surface area measurements, samples were dried in a vacuum oven (Model 68351, Precision Scientific Co., Chicago, IL, U.S.A.) at 60°C and at a reduced pressure of 40mmHg for 24h. Samples were then degassed for 24h under continuous nitrogen flow. A five point Brunauer, Emmett and Teller (BET) analysis was conducted on all samples, by performing the N<sub>2</sub> adsorption and desorption at

relative pressures ( $P/P_0$ ) ranging from 0.05 to 0.25.

**Preparation of Tablets** Approximately, 500mg of powder was compressed on a single station tablet press (Model C, Carver Press, Menomonee Falls, WI, U.S.A.) at pressures ranging from 10 to 260MPa using a 13mm round flat-faced tooling and a dwell time of 30s. The upper punch was equipped with a load cell (Model: LCGD-10K, Range 0–10000lbs, Omega Engineering, Inc., Stamford, CT, U.S.A.) and a strain gauge meter (Model: DP25B-S, Omega Engineering, Inc., Stamford, CT, U.S.A.). Tablets were kept in a desiccator over Drierite for 48h before the analysis.

**Compressibility Analysis** Compact volume 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, U.S.A.). Compact densification data were fitted to the Heckel and Kawakita models. Heckel<sup>12)</sup> proposed a model for powder compressibility, which is given by:

$$\ln(1/\varepsilon) = kP + A \quad (1)$$

Where,  $\varepsilon$  is the porosity of the compact at a pressure  $P$  and  $A$  the intercept it represents the powder densification by die filling and particle rearrangement before deformation and bonding of particles took place. The slope ( $k$ ) of the linear portion of the plot is inversely related to the mean yield pressure ( $P_y$ ), which is a measurement of the plasticity of the compressed material.<sup>13,14)</sup> The Kawakita model on the other hand, describes the relationship between the degree of volume reduction of the powder and the applied pressure.<sup>15)</sup> The Kawakita model is given by:

$$P/C = P/a + 1/ab \quad C = 1 - \rho_0/\rho_a \quad (2)$$

Where,  $\rho_a$ ,  $\rho_0$ ,  $C$ , 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.<sup>16)</sup>

**Compact Tensile Strength (TS) and Energy at Break** A Q-test I universal tester (Model, QT-1, MTS, System Corp., Eden Prairie, MN, U.S.A.) was employed. Cylindrical compacts were prepared as describe under “Preparation of Tablets” at a 0.2 porosity. The force-deformation curves were obtained using the Testworks QT software v. 2.03 (MTS, System Corp., Eden Prairie, MN, U.S.A.) and the compact energy at break was determined from the area under the curve of such curves. The crosshead speed of the upper platen was kept constant at 0.01 mm/s. TS values were obtained according to the Fell and Newton equation from the force at break given by the load-deformation curves.<sup>17)</sup>

**Compact Elastic Recovery** Compacts were made as described under “Preparation of Tablets” at a compression pressure of 100MPa. Compact heights were measured once ejected and stored in a desiccator over Drierite<sup>®</sup> and after five days compacts heights were measured again. The compact elastic recovery was expressed as percentage.

**Lubricant Sensitivity** Silicified materials and magnesium stearate (1% w/w) were mixed using a twin shell blender (Model LB429, The Petterson Kelley Co. East Stroudsburg, PA, U.S.A.) for 30min. Compacts (*ca.* 500mg) were made at

60 MPa compression pressure and dwell time of 30 s. Lubricant sensitivity was expressed as a ratio (LSR) according to the relationship:  $LSR = (S_0 - S_{lub}) / S_0$ , where  $S_0$  and  $S_{lub}$  are the crushing strengths of tablets prepared without and with lubricant, respectively.

**Disintegration Studies** Disintegration tests were performed in distilled water according to the USP 28/NF23 specifications, employing an Eureka GmbH disintegration apparatus (Type 712, Erweka, Offenbach, Germany).<sup>18)</sup>

**Griseofulvin Release Studies** Griseofulvin, which is a poorly water soluble drug (0.0346 mm) was used as a model drug. Compacts were made by mixing 125 mg of griseofulvin and 375 mg of silicified excipients on a mortar and pestle for 10 min followed by compression at 120 MPa. The USP UV method was employed.<sup>18)</sup> Aliquots were diluted in a methanol:water (4:1) solvent and analyzed by UV-VIS Spectrophotometry (Hewlett Packard, Model 8453, Isco, Inc., Lincoln, NE, U.S.A.). The dissolution study was performed using the apparatus 2 (Pharma Test, Scientific Instruments and Technology Corp., Piscataway, NJ, U.S.A.) 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 1 mL aliquots of the dissolution medium.

## Results and Discussion

Figures 1 and 2 show the SEM images of processed and silicified materials respectively. MCCII has a fibrous nature as obtained from cotton linters without any further processing.

Prosolv<sup>®</sup> SMCC 50 and Prosoolv<sup>®</sup> SMCC 90 are spray-dried CI:SiO<sub>2</sub> composites at a ratio 98:2 and appear as aggregates. Although it is not evident by the microphotographs, it is reported that tiny SiO<sub>2</sub> aggregates are homogeneously distributed on the surface of cellulose I and possibly, in the core of Prosoolv<sup>®</sup> making its surface rougher and showing an irregular shape.<sup>10)</sup> Spray-dried materials appear as oblong particles and small in size (*ca.* 50 μm) whereas wet granulated materials appear as granules of a larger size (*ca.* 100 μm). These characteristics show that processing and silicification of cellulose had a major effect on particle morphology and surface characteristics, respectively. Granules consist of aggregates with rough surfaces and presented an irregular shape. Partial SiO<sub>2</sub> deposition on the surface was characteristic of those granules. Further, it is also possible that some of the SiO<sub>2</sub> particles penetrated into the core of the granules.

Table 1 shows selected properties for silicified cellulosic materials. Silicification increased powder porosity and hence decreased the bulk density of processed MCCII. Further, silicification contributed largely to compactibility due to the large contribution in particle surface area which is available for binding. It is possible that during consolidation the increasing levels of fumed silica particles in the powder bed causes an initial large rearrangement due to SiO<sub>2</sub> deaggregation and probably extensive fragmentation of the particles in which small fumed silica particles fill in the void spaces between the large MCCII particles. At large compression pressures, more deaggregation, creation of new surfaces and movement

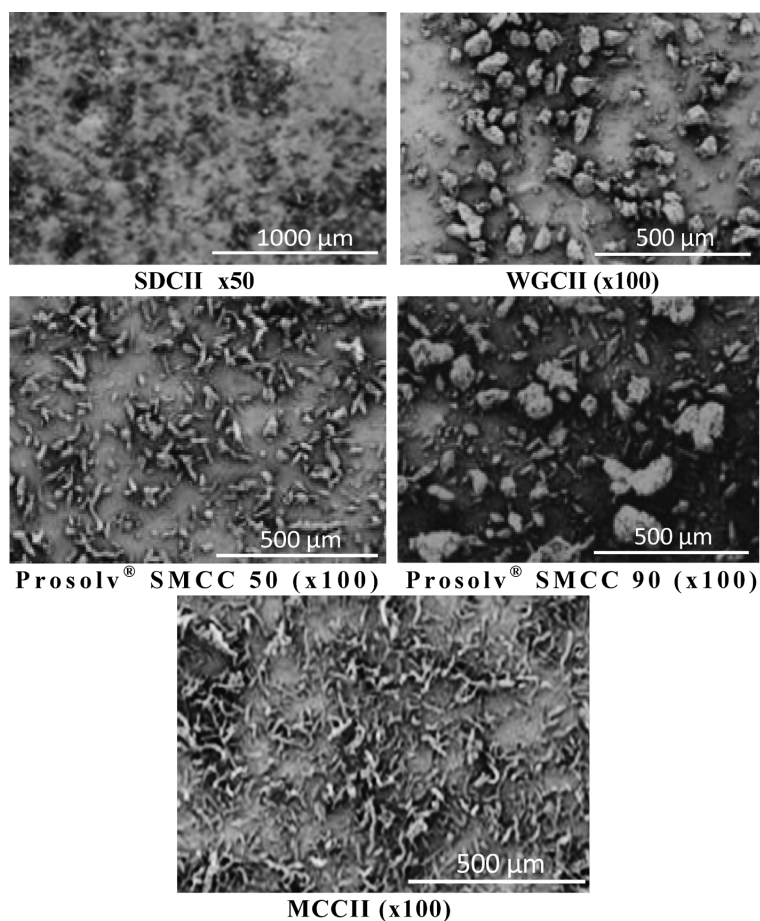


Fig. 1. SEM of the MCCII, SDCII, WGCII and Commercial Products

of fumed silica particles along with the MCCII crystal planes dislocation may cause a larger compact rigidity than that produced by MCCII alone. Surprisingly, the mere spray drying and wet granulation of MCCII also improved its compactibility. However, this increase was not as prominent as the one caused by silicification through spray drying and wet granulation. Comparing tensile strength and energy at break values of

compacts, spray-dried materials showed higher compactibility than wet granulated products. This finding was accompanied with an increase in compact deformation and can be attributed to particle interactions of MCCII with SiO<sub>2</sub>.

Compacts of Prosolv<sup>®</sup> SMCC 50 and Prosolv<sup>®</sup> SMCC 90 required the highest energy at break followed by silicified MCCII materials. It is reasonable that these highly plastic deforming materials which produced stronger compacts required a higher energy to dislocate the crystal planes and ultimately cause a tablet failure than the energy needed for the less plastic deforming silicified MCCII materials. Wet granulated materials showed lower energy at break values compared to spray-dried materials.

Heckel suggested that the rate of change of porosity in the powder bed with pressure follows a first order kinetics. He established that compaction of powdered samples (given by porosity–pressure curves) follows a three-stage process: die filling, individual particle motion and gross compact deformation.<sup>12)</sup> The linear region of the Heckel plot allows for the interpretation of the deformation mechanism. From the inverse of the slope and the intercept the yield pressure,  $P_y$  and the total powder densification at low pressures are obtained. A material with a lower  $P_y$  value is expected to be more ductile.

Table 2 lists the resulting Heckel parameters for silicified MCCII materials. Compared to MCCII and SDCII (spray-dried cellulose II) which had  $P_y$  of 115 MPa and 119 MPa, respectively, all silicified materials exhibited larger  $P_y$  values. This phenomenon might be caused by the SiO<sub>2</sub> aggregates; once compression starts, these particles deaggregate and rearrange around MCCII probably decreasing the apparent plastic deformation taking place in the powder bed.

The  $D_0$  value, which indicates the initial packing ability of the material in the die, suggests that as the amount of SiO<sub>2</sub> in the composite increases, the packing ability of MCCII decreased due to decreasing densification tendency. This result is in agreement with the trend observed for the bulk density. Furthermore, both MCCII and Prosolv<sup>®</sup> SMCC 50 exhibited a low packing tendency similar to that of SDCII:SiO<sub>2</sub> (80:20). These results are consistent considering the very low bulk density and high porosity of these materials ( $\rho_{\text{bulk}}$ , 0.32–0.38 g/

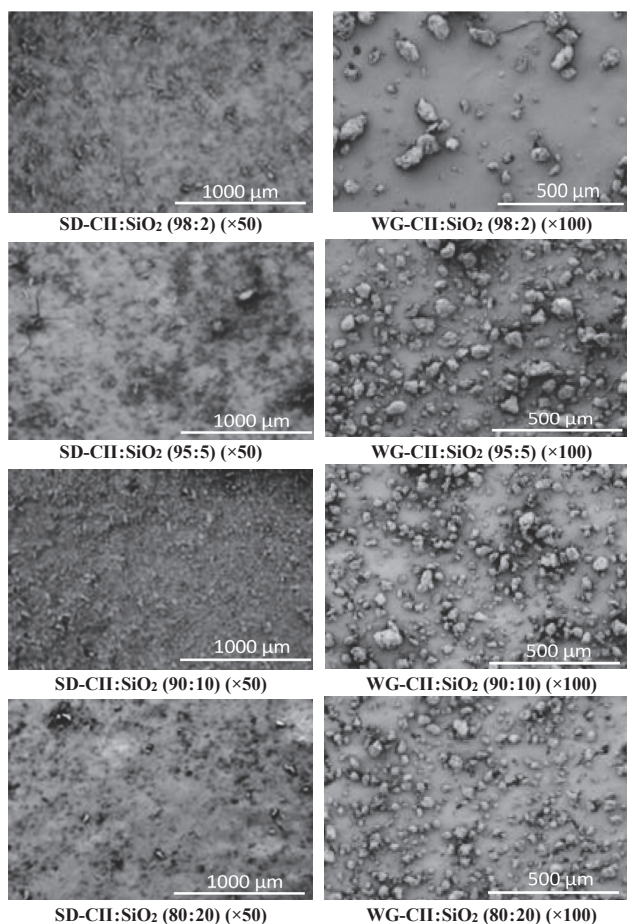


Fig. 2. SEM of the Silicified Materials

Table 1. Selected Properties of Silicified MCCII Materials

| Sample                          | Powder porosity<br>$n=1$ | Bulk density (g/cc)<br>$n=3$ | Specific surface area<br>(m <sup>2</sup> /g)<br>$n=3$ | Compact tensile strength<br>(MPa) <sup>a)</sup><br>$n=3$ | Energy at break<br>(J×10 <sup>-2</sup> ) <sup>a)</sup><br>$n=3$ |
|---------------------------------|--------------------------|------------------------------|---|--|---|
| MCCII                           | 0.76                     | 0.38±0.03                    | 0.52±0.06   | 0.5±0.0  | 0.3±0.0   |
| SD-CII:SiO <sub>2</sub> (80:20) | 0.78                     | 0.36±0.00                    | 41.36±1.43  | 7.7±0.0  | 5.8±0.5   |
| SD-CII:SiO <sub>2</sub> (90:10) | 0.73                     | 0.42±0.01                    | 20.91±0.36  | 6.0±0.0  | 4.6±0.4   |
| SD-CII:SiO <sub>2</sub> (95:5)  | 0.7                      | 0.45±0.00                    | 10.46±0.14  | 4.5±0.0  | 3.9±0.3   |
| SD-CII:SiO <sub>2</sub> (98:2)  | 0.69                     | 0.48±0.01                    | 3.94±0.05   | 3.6±0.0  | 2.9±0.7   |
| SDCII                           | 0.64                     | 0.55±0.00                    | 1.59±0.04   | 2.5±0.0  | 1.0±0.0   |
| Prosolv <sup>®</sup> SMCC50     | 0.79                     | 0.32±0.00                    | 6.32±0.05   | 7.5±0.0  | 14.8±3.9  |
| WG-CII:SiO <sub>2</sub> (80:20) | 0.66                     | 0.28±0.00                    | 28.34±1.29  | 4.4±0.0  | 3.7±1.0   |
| WG-CII:SiO <sub>2</sub> (90:10) | 0.63                     | 0.55±0.00                    | 16.23±0.10  | 3.4±0.0  | 3.0±0.0   |
| WG-CII:SiO <sub>2</sub> (95:5)  | 0.61                     | 0.58±0.00                    | 6.63±0.07   | 2.2±0.0  | 2.6±0.5   |
| WG-CII:SiO <sub>2</sub> (98:2)  | 0.59                     | 0.61±0.01                    | 1.12±0.14   | 1.2±0.0  | 1.4±0.2   |
| WGCII                           | 0.76                     | 0.64±0.03                    | 0.39±0.01   | 1.2±0.0  | 1.0±0.1   |
| Prosolv <sup>®</sup> SMCC90     | 0.82                     | 0.28±0.00                    | 5.46±0.01   | 6.9±0.0  | 7.6±0.5   |
| <i>p</i> -Value                 | N.A. <sup>b)</sup>       | 0.00                         | 0.00  | 0.00   | 0.00  |

a) Compacts made at 0.2 porosity. b) Not applicable.

Table 2. Heckel Parameters for Silicified MCCII Materials

| Product                          | Pressure range (MPa) | Heckel parameters |      |       |       |       |        |
|----------------------------------|----------------------|-------------------|------|-------|-------|-------|--------|
|                                  |                      | $P_y$ (MPa)       | $A$  | $D_0$ | $D_a$ | $D_b$ | $r^2$  |
| MCCII                            | 90–175               | 115               | 1.68 | 0.24  | 0.81  | 0.57  | 0.9880 |
| SDCII                            | 65–120               | 119               | 1.25 | 0.36  | 0.72  | 0.36  | 0.9990 |
| SD-CII: SiO <sub>2</sub> (98:2)  | 65–150               | 161               | 1.28 | 0.31  | 0.72  | 0.41  | 0.9972 |
| SD-CII: SiO <sub>2</sub> (95:5)  | 65–175               | 150               | 1.03 | 0.29  | 0.64  | 0.37  | 0.9940 |
| SD-CII: SiO <sub>2</sub> (90:10) | 90–175               | 179               | 1.00 | 0.26  | 0.63  | 0.37  | 0.9810 |
| SD-CII: SiO <sub>2</sub> (80:20) | 65–120               | 182               | 0.78 | 0.22  | 0.54  | 0.32  | 0.9888 |
| Prosolv <sup>®</sup> SMCC50      | 35–125               | 98                | 0.74 | 0.21  | 0.52  | 0.31  | 0.9976 |
| WGCII                            | 65–175               | 91                | 0.98 | 0.41  | 0.62  | 0.21  | 0.9917 |
| WG-CII: SiO <sub>2</sub> (98:2)  | 35–120               | 102               | 0.78 | 0.39  | 0.54  | 0.15  | 0.9994 |
| WG-CII: SiO <sub>2</sub> (95:5)  | 35–175               | 112               | 0.77 | 0.37  | 0.54  | 0.17  | 0.9967 |
| WG-CII: SiO <sub>2</sub> (90:10) | 35–150               | 120               | 0.77 | 0.34  | 0.53  | 0.19  | 0.9990 |
| WG-CII: SiO <sub>2</sub> (80:20) | 11–120               | 147               | 0.59 | 0.17  | 0.45  | 0.28  | 0.9957 |
| Prosolv <sup>®</sup> SMCC90      | 90–175               | 108               | 0.74 | 0.18  | 0.52  | 0.34  | 0.9949 |

$A$ , Powder total densification;  $D_0$ , relative density due to die filling;  $D_b$ , relative density due to particle rearrangement/fragmentation.

Table 3. Kawakita Parameters of Silicified MCCII Materials

| Product                          | Ejection force (kN) $n=3$ | Elastic recovery (%) | Kawakita parameters |      |        |
|----------------------------------|---------------------------|----------------------|---------------------|------|--------|
|                                  |                           |                      | $a$                 | $b$  | $r^2$  |
| MCCII                            | 0.24±0.02                 | 11.7±0.5             | 0.76                | 0.31 | 1.0000 |
| SDCII                            | 0.59±0.06                 | 10.2±1.5             | 0.63                | 0.14 | 0.9999 |
| SD-CII: SiO <sub>2</sub> (98:2)  | 0.38±0.05                 | 7.1±0.1              | 0.68                | 0.17 | 0.9999 |
| SD-CII: SiO <sub>2</sub> (95:5)  | 0.46±0.03                 | 6.1±0.6              | 0.70                | 0.14 | 0.9999 |
| SD-CII: SiO <sub>2</sub> (90:10) | 0.51±0.05                 | 3.6±0.7              | 0.73                | 0.12 | 0.9995 |
| SD-CII: SiO <sub>2</sub> (80:20) | 0.85±0.04                 | 1.7±0.5              | 0.76                | 0.15 | 0.9998 |
| Prosolv <sup>®</sup> SMCC50      | 0.04±0.01                 | 0.5±0.5              | 0.78                | 0.15 | 1.0000 |
| WGCII                            | 0.61±0.06                 | 5.1±0.4              | 0.60                | 0.09 | 0.9998 |
| WG-CII: SiO <sub>2</sub> (98:2)  | 0.28±0.03                 | 4.2±0.8              | 0.62                | 0.06 | 0.9996 |
| WG-CII: SiO <sub>2</sub> (95:5)  | 0.33±0.05                 | 3.6±0.4              | 0.63                | 0.07 | 0.9995 |
| WG-CII: SiO <sub>2</sub> (90:10) | 0.73±0.05                 | 3.3±0.3              | 0.65                | 0.08 | 0.9997 |
| WG-CII: SiO <sub>2</sub> (80:20) | 0.87±0.05                 | 2.7±0.4              | 0.81                | 0.19 | 0.9999 |
| Prosolv <sup>®</sup> SMCC90      | 0.10±0.02                 | 1.0±0.6              | 0.83                | 0.18 | 1.0000 |
| $p$ -Value                       | 0.00                      | 0.00                 | N.A.                | N.A. | N.A.   |

$a$ , Compressibility parameter;  $b$ , indicates ease of compression.

cm<sup>3</sup> and porosity, 0.76–0.79). The parameters  $D_a$  and  $D_b$  represent the total packing and the extent of powder bed arrangement due to particle fragmentation/rearrangement at low pressures, respectively. These results indicate that total densification and densification by die filling ( $D_a$  and  $D_0$ , respectively) of the materials decreased as the silicification level increased. Interestingly, the fibrous MCCII had a large effect on  $D_a$  since this material showed the largest  $D_b$  suggesting that these fibers were able to rearrange extensively, filling up the interparticle voids in the powder bed at low pressures and consequently, packed better at low applied pressures. Except for SDCII, the rearranging behavior ( $D_b$ ) of silicified spray-dried MCCII materials and Prosol<sup>®</sup> SMCC 50 was more prevalent than the simple packing behavior (given by the  $D_0$  values). This indicates that at low pressures silicification caused particles to deaggregate extensively and rearrange/fragment in the powder bed. Likewise, compared to WGCII (wet granulated cellulose II), all silicified materials and granulated materials showed higher  $P_y$  values (91 MPa vs. 102–147 MPa), suggesting that silicification could increase brittleness in the powder bed due

particle rearrangement and deaggregation of fumed silica aggregates. The process employed *per se* caused changes in the  $P_y$  value of MCCII. For instance, MCCII had a higher  $P_y$  than WGCII, but comparable  $P_y$  than SDCII. This indicates that the deformation mechanism is not altered for MCCII if a rapid drying is conducted as opposed to wet granulation. Perhaps part of water used during wet granulation is not completely given up upon slow drying and hence, this non-free water could induce some apparent plasticity in MCCII. Prosol<sup>®</sup> SMCC 90 which has a 2% SiO<sub>2</sub> had a  $P_y$  of 108 MPa. Typical  $P_y$  values for cellulose I materials are between 40 to 80 MPa as reported previously.<sup>19)</sup> The yield pressure value for cellulose I materials such as Prosol<sup>®</sup> SMCC 50 was 93 MPa. Researchers have reported that a 2% SiO<sub>2</sub> in cellulose I virtually does not affect  $P_y$ .<sup>20,21)</sup>

As seen for the spray-dried materials, the total initial compact densification ( $D_0$ ) decreased significantly at the 20% silicification level due to the decreasing powder densification. Moreover, the  $D_0$  parameter decreased progressively from 0.41 to 0.17 upon silicification, whereas  $D_b$  increased. For

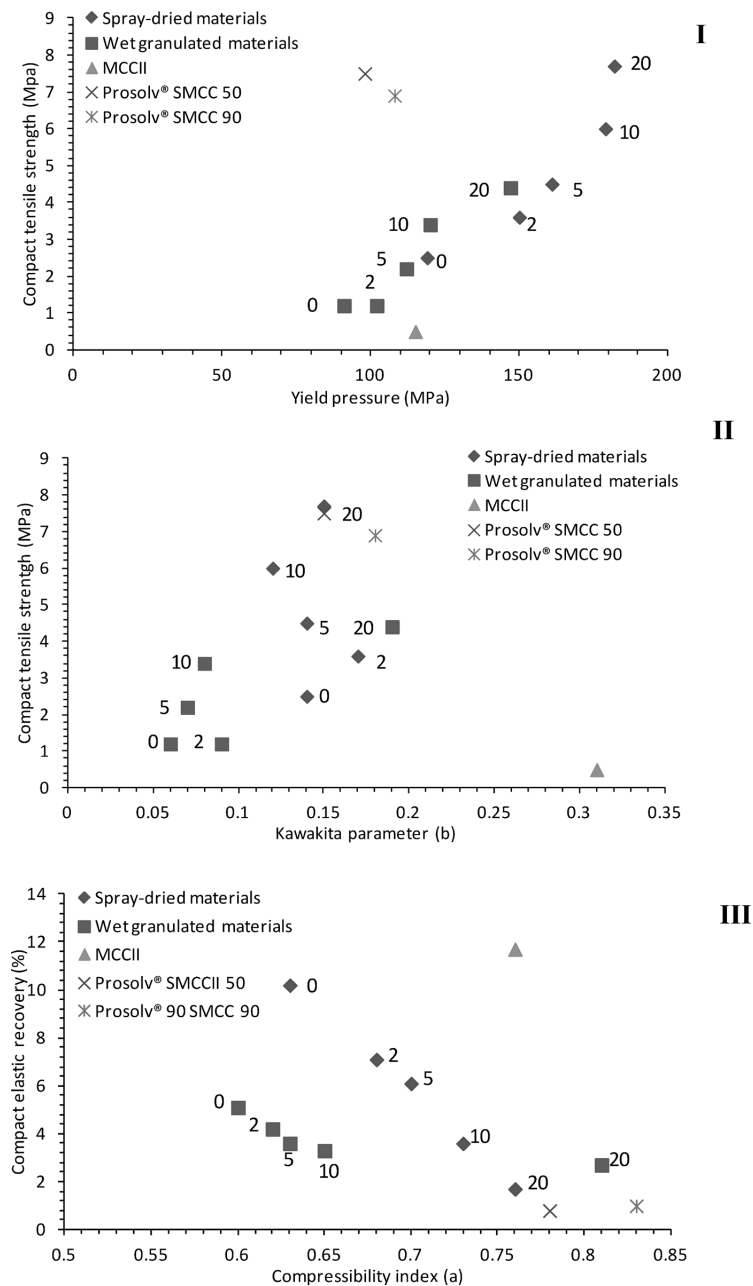


Fig. 3. Relationship between Tensile Strength and (I) Yield Pressure, the Kawakita (b) Parameter (II), and (III) between Elastic Recovery and Compressibility Index for Materials at 0–20% Silicification

this reason, compared to spray-dried powders, wet granulated materials, due to their high particle densities, had a more prevalent densification by die filling than densification by particle rearrangement, except for the 20% silicification. Compared to the spray-dried materials, wet granulated materials had lower  $D_b$  and  $P_y$  values, indicating that they undergo less powder rearrangement/fragmentation. Likewise,  $D_a$  values of spray-dried materials were larger than those obtained for wet granulated materials, suggesting spray drying induced a high powder densification, especially due to rearrangement/fragmentation. Further, when  $P_y$  was larger than 147 MPa in silicified MCCII materials,  $D_b$  was larger than  $D_0$  indicating extensive rearrangement/fragmentation taking place within the powder bed.

The Kawakita model describes the variation of powder volume reduction with compression pressure in a linear

relationship. In this case, the inverse of the slope called compressibility index or “ $a$ ” corresponds to the volume reduction ability of the material, whereas from the intercept the “ $b$ ” parameter is obtained, and represents the ease of compression. The Kawakita parameters are given in Table 3. The compressibility parameter “ $a$ ” indicates that silicification enhanced the compressible character of the materials. This could be attributed to a lowering densification effect caused by silicification forming more void spaces between particles. Further, the “ $a$ ” parameter and the total powder porosity were comparable, as reported previously.<sup>22)</sup> For example, MCCII, SD-CII-80:20, and ProsoIv® SMCC 50, had bulk densities of 0.38 g/cm<sup>3</sup>, 0.36 g/cm<sup>3</sup>, and 0.32 g/cm<sup>3</sup>, respectively, which were translated in a high compressibility (“ $a$ ” value of 0.76, 0.76, 0.78, respectively), and porosity values (0.76, 0.78, 0.79, respectively). On the other hand, as discussed previously,

SDCII was the least compressible material due to its high bulk density, low porosity and less fragmenting behavior. The “*b*” value obtained from the Kawakita analysis has been inversely related to cohesion and other type of particle interaction forces.<sup>23,24</sup> The highest “*b*” parameter obtained for MCCII suggests a low degree of interparticle interactions that oppose volume reduction, and hence, this material was the easiest to compress. All spray-dried materials, in contrast, showed low “*b*” values (0.12 to 0.17), indicating more interparticle interactions to overcome during compression due to the combined effect of silicification and the high densification caused by spray drying. Table 3 also shows the Kawakita parameters for the wet granulated materials. The “*a*” compressibility index progressively increased with silicification, indicating a high volume reduction with silicification, as discussed previously. It is possible that SiO<sub>2</sub> aggregates rearrange and fragment in the powder bed around MCCII particles, leading to improved packing. Powder porosity and “*a*” values were comparable and inversely related to the bulk density as seen for the spray-dried materials. The “*b*” values increased slightly with silicification especially at the 20% level suggesting this material as the easiest to compress. Moreover, for wet granulated materials, a larger degree of interparticulate interaction has to be overcome in order to get the same degree of volume reduction than spray-dried materials.

Figure 3I shows a relationship between compact tensile strength and yield pressure. Independent of the process employed, silicification increased compact tensile strength and powder yield pressure. This means that the onset of apparent plastic deformation increased with silicification. This is explained by the fumed silica aggregates which fragment and percolate in the powder bed and the increasing of surface area and hence bonding available to form strong compacts. Tensile strength of cellulose I materials on the other hand, was always high despite of their characteristic low yield pressure. Figure 3II shows the variation of tensile strength with the Kawakita “*b*” parameter. This value barely changed with silicification for the spray-dried materials, but increased at the 20% silicification for the wet granulated materials indicating ease of compression at this level due to the bulky nature of fumed silica. Further, tensile strength was larger for silicified materials and was not correlated to the “*b*” parameter. This means that this parameter was more related to particle morphology rather than to silicification.

Silicification increased the ejection forces of the upper punch in the spray-dried (0.38–0.85 kN) and wet granulated materials (0.28–0.87 kN). This is attributed to the frictional forces between the die wall and the brittle deforming fumed silica. The addition of a lubricant should be considered for such materials. On the other hand, cellulose I materials such as Prosolv<sup>®</sup> exhibited the lowest friction, attributable to their known high plastic deforming ability and low surface area. Cellulose I materials also had high “*a*” compressibility values and a low degree of interparticle interactions “*1/b*” indicating ease of compression and thus, required lower applied compression pressures to produce a significant volume reduction. Further, fumed silica, which caused an increase in particle surface area and especially SiO<sub>2</sub> aggregates located at the compact edges, is more likely to deaggregate and create friction causing perpendicular resistant forces, impeding the axial ejection of the compact. On the other hand, the addition of a

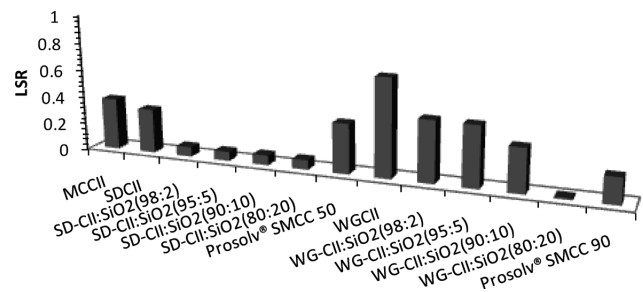


Fig. 4. Lubricant Sensitivity of Silicified MCCII Materials

lubricant can fill the gaps between the detached fragments and reduce the contact points between the compact and the die wall surfaces easing compact ejection and decreasing die wear due to abrasion.

Elastic recovery occurs when part of the energy applied for compaction instead of causing permanent plastic or brittle deformation is released in the form of elastic rebound. The elastic recovery of spray-dried and wet granulated compacts is depicted in Table 3. The data represent only the out-of-die results for compacts immediately released from the die compared to the respective height five days after storage under Drierite<sup>®</sup> in a desiccator at room temperature. For this reason, these data only represent the slow time-dependent elastic recovery since the in-die fast elastic component was not determined due to technical limitations. Silicification reduced the elastic relaxation tendency of MCCII and this tendency was more pronounced at high silicification levels. Perhaps, silicification, by increasing surface area and particle rearrangement in the powder bed, allowed more permanent particle bonding preventing energy release from MCCII bonded particles. Thus, silicification prevented agglomerate particles to expand avoiding axial volume increase in the compact improving compact strength. The reduction of elastic recovery was more efficient in spray-dried materials than in wet granulated products suggesting that when SiO<sub>2</sub> is coating completely MCCII particles, a stronger compact is formed due to the resulting high surface area available for bonding. Further, a low elastic recovery behavior was also characteristic for cellulose I products since they formed stronger compacts with virtually no variation of this property with compression pressure. Figure 3III shows the variation of compact elastic recovery with the compressibility index. In all cases the elastic recovery decreased with silicification and compressibility index or porosity as explained previously.

As seen in Fig. 4, the lubricant sensitivity expressed as the lubricant sensitivity ratio (LSR) to magnesium stearate was low for all silicified MCCII composites (*ca.* 0.05). On the other hand, a 2% SiO<sub>2</sub> in Prosolv<sup>®</sup> SMCC 50 had a minimum counteracting effect on magnesium stearate due to its known high plastic behavior. It must be remembered that this material also had a low *P<sub>y</sub>* value of 98 MPa. These results suggest that materials with a low *P<sub>y</sub>* value such as Prosolv<sup>®</sup> SMCC 50 were more sensitive to magnesium stearate, and the sensitivity decreased as the SiO<sub>2</sub> level increased. Other reported studies have found an inverse relationship between plasticity and lubricant sensitivity for Avicel<sup>®</sup> products.<sup>25,26</sup> The low sensitivity of silicified MCCII materials to magnesium stearate is due to particle coating by SiO<sub>2</sub>, for which magnesium stearate competes during compression. Thus, the presence of

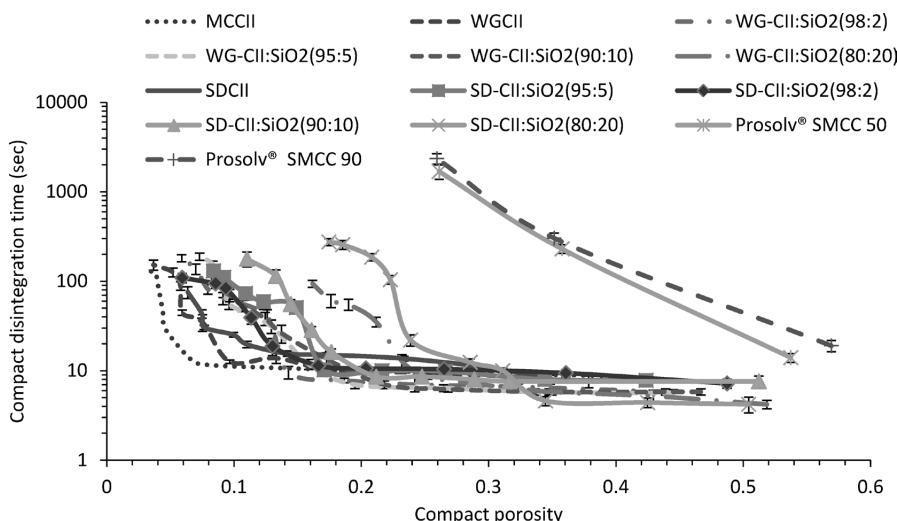


Fig. 5. Compact Disintegration of Silicified MCCII Materials

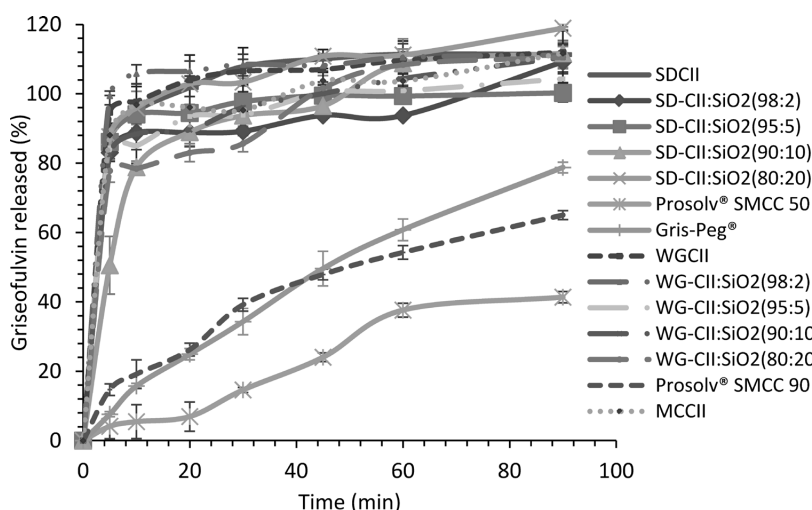


Fig. 6. Release Studies of Griseofulvin from Silicified MCCII Materials

$\text{SiO}_2$  creates a more fragmenting behavior forming new clean surfaces available for binding with less lubricant sensitivity. Opposite to the results seen for the spray-dried materials, silicification using wet granulation did not decrease lubricant sensitivity considerably except at 20% silicification. The partial surface coverage by  $\text{SiO}_2$  compared to spray-dried materials might be responsible for this, since  $\text{SiO}_2$  in the granules core is not completely available to interact with magnesium stearate. WG-CII was more sensitive to magnesium stearate than MCCII. This is in agreement with the lower  $P_y$  values obtained for WG-CII (91 MPa) as discussed previously.

Among cellulose I materials, Prosolv® SMCC 90 had lower lubricant sensitivity than silicified wet granulated materials because of the fragmenting behavior of  $\text{SiO}_2$  located on the surface which produced some free surfaces available for binding. Further, Prosolv® SMCC 90 had higher  $P_y$  than Prosolv® SMCC 50 (108 MPa vs. 98 MPa), and was less sensitive to magnesium stearate confirming the inverse relationship between yield pressure and lubricant sensitivity. It has been reported previously that silicified cellulose I materials (Prosol®) are less sensitive to magnesium stearate than the unsilicified ones.<sup>21,27</sup>

Figure 5 shows the fast disintegrating properties of silicified materials made by spray drying and wet granulation, respectively. Results indicate that independent of the process employed, all silicified MCCII materials showed faster disintegration times compared to cellulose I products. At low porosities curves are shown as flat lines up to a point where disintegration times increase sharply. This point is defined as a critical porosity below which disintegration time increased significantly. This critical porosity increased with increasing silicification levels. Beyond the critical porosity, compact disintegration time increased mainly due to the high contribution of silicification on compact strength and perhaps, the decrease in water affinity caused by fumed silica (especially at 20% level) which reduced interactions with water compared to MCCII particles as reported previously.<sup>10</sup> MCCII which is unsilicified, showed the lowest critical porosity (0.06) indicating that the absence of fumed silica favored compact disintegration due to the formation of less strong compacts and the high affinity of MCCII for water. Prosolv® SMCC 50 and Prosolv® SMCC 90 compacts beyond 0.26 porosities presented a steady decrease of disintegration time. Below this porosity, these compacts did not disintegrate during the test period (*ca.*



300 min). Long disintegration times were expected for these materials since they showed the highest compactibility by forming strong compacts with low affinity for water.

Figure 6 shows the griseofulvin release results for the spray-dried and wet granulated compacts, respectively. Drugs were released from compacts of *ca.* 500 mg having a diameter of *ca.* 1.3 cm. The drug content per tablet was 125 mg. All silicified MCCII materials released more than 75% of griseofulvin within 10 min. On the other hand, Prosolv<sup>®</sup> SMCC 50, Prosolv<sup>®</sup> SMCC 90 and Gris-Peg<sup>®</sup> compacts released 18%, 10% and 16% within 10 min. Further, Gris-Peg<sup>®</sup> barely fulfilled the 75% release requirement specified in the USP28/NF23 within the 90 min of the test. Further, compacts of cellulose I materials did not pass the test due to the formation of strong compacts. These results suggest that highly binding materials with less water affinity than MCCII are not appropriate to formulate poorly water-soluble drugs because compact disintegration and further water accessibility to the compact are restricted and thus, drug dissolution is delayed. In these cases, a disintegrant, along with a non-hydrophobic lubricant is required.

### Conclusions

Silicified materials produced by spray drying and wet granulation had better binding properties than unsilicified MCCII. Silicification increased compressibility, decreased densification by die filling at initial stages of compression and decreased the plasticity of MCCII. It also decreased MCCII susceptibility to lubricants, especially when spray drying was employed. Moreover, silicification did not affect the fast disintegration and the rapid release of griseofulvin compared to Prosolv<sup>®</sup> SMCC products. Further, silicification decreased the elastic recovery tendency of MCCII due to the increase in specific surface area of the particles improving contact points among particles and hence compactibility. These new silicified MCCII materials offered potential for use as multifunctional (a binder, a filler and a disintegrant) direct compression excipient, all-in-one, in the design and development of solid dosage forms, especially to formulate rapidly disintegrating tablets.

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