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COMMUNICATION

Physicochemical and Mechanical Evaluation of a Novel High Density Grade of Silicified Microcrystalline Cellulose

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ABSTRACT

High density microcrystalline cellulose (MCC) is a relatively free flowing grade of MCC that finds use in direct compression tableting and hard gelatin capsule filling applications. Silicified high density microcrystalline cellulose has recently been introduced. This material has been compared to other grades of MCC and previously silicified microcrystalline cellulose (SMCC). The results suggest that, as observed for other grades of SMCC, the material exhibits no detectable chemical or polymorphic differences to standard material, some improvement in flow characteristics, but shows considerably enhanced mechanical properties.

Key Words: Silicified MCC; MCC; Prosolv; High density MCC; Mechanical properties.

INTRODUCTION

Microcrystalline cellulose (MCC) is widely used as a filler/binder in solid dosage forms and has been rated as the leading filler/binder choice for direct compression.[1] However, its relatively low bulk density and poor flow can result in poor tablet weight uniformity and segregation during dry blending, which has limited its use in some applications, for example, with poorly flowing drugs. Additionally, its relatively high strain rate sensitivity may also limit use in some high-speed tableting applications.[1]

In order to address the problem of the relatively poor flow and low bulk density of conventional grades of MCC, manufacturers have produced and marketed high density (HD) grades of MCC as an alternative material for capsule filling and direct compression.

These products are manufactured in a similar way to regular grades but are produced from hardwood rather than softwood sources. These HD materials exhibit

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subtle differences in physicochemical characteristics such as crystallinity, surface area, and porosity compared to regular grades of MCC. These grades, when compared with conventional materials of a similar particle size, have improved flow characteristics, leading to improved weight uniformity in direct compression or capsule fill operations, compared to conventional grades, although there have been few reports describing their mechanical performance.

It is generally accepted, nevertheless, that high density MCCs exhibit poorer binding properties, and, as a consequence of their reduced surface area, greater sensitivity to lubricants. A recently introduced low density grade of MCC, Ceolus™ (Asahi Kasei Corp., Osaka, Japan), has been reported to possess improved binding properties when compared with conventional MCCs.[2,3] This suggests that there is a relationship, if not a simple one, between the density of an MCC material, its binding properties, and associated mechanical characteristics.

High density silicified microcrystalline cellulose (HD SMCC) has recently become commercially available. A limited number of studies have been published describing this material and none have discussed its specific mechanical properties.[4–7] However, some studies have reported that this new material shows enhanced flow properties when compared with conventional materials, both as a bulk material and in limited tableting operations.[4,5]

Previous studies have reported that the silicification process, when applied to other grades of MCC, does not change the physicochemical properties[8] of the material but improves its mechanical performance,[9] flow properties, and lubricant sensitivity.[10] These materials are gaining wider acceptance.[11]

In this study we present a physicochemical evaluation of this material and utilize recently developed techniques to establish its mechanical properties in comparison with previously available materials.

EXPERIMENTAL

Emcocel HD90 (batch no. HD9B5K3), Emcocel 90M (batch no. E9B8A01), and Prosolv HD90 (HD SMCC, batch no. K9S9040) were used as supplied (Penwest Co., Danbury, CT, NY).

Solid State Nuclear Magnetic Resonance Spectroscopy (SS NMR)

Solid state cross polarization magic angle spinning NMR spectra were collected using a Varian UNITY *Inova* (University of Durham) operating under a static field of 7.05 T. Samples were packed into a 7-mm probe with $(CH_3)_4Si$ as reference. The following conditions were used: spin rate 4500 Hz; radio frequency field strength ($\gamma B_1/2\gamma$) were 75.43 MHz; 300 acquisitions; 20.0 ms acquisition time; 4 sec relaxation delay; and cross polarization with flip-back.

Physical Characterization of Powders

Particle Size Analysis

Particle size distribution analysis by laser diffraction was performed using the Mastersizer 2000 (Malvern Ltd., Malvern, UK). Samples were presented as dry powders using the Scirocco 2000 automated dry powder feeder set to yield a pressure drop of 3 bar across the sampling chamber. Each analysis is the mean of 10,000 scans over 10 seconds. Sample feed rate was adjusted to give a laser obscuration of 0.5% to 2.0% during analysis. The results from three repeat analyses are shown.

Tapped and Bulk Density

Samples of the powders (25 g) were carefully poured into a measuring cylinder (50 mL). The measuring cylinder was stoppered and the bulk density recorded. The cylinder was tapped 2000 times (no change in tapped density was detected after 2000 taps) using a jolting volumeter (J. Engelsmann, Ludwigshafen, Germany) and the tapped density recorded. Carr's compressibility index was calculated from the bulk and tapped densities.[12]

Surface Area

Surface areas were determined by 5-point BET N_2 adsorption using the Gemini 2360 nitrogen adsorption apparatus (Micromeritics, Norcross, GA). After loading into the analysis vessel, the samples were dried at 40° C to constant mass (16–20 hours) under a stream of dry nitrogen using the FlowPrep 060 (Micromeritics, Norcross, USA). This drying regime was validated by monitoring the sample mass over drying periods of 1 to 24 hours. The partial pressure of N_2 was adjusted by mixing the analysis gas with helium, to a maximum partial pressure of 0.2.

Scanning Electron Microscopy

Samples were coated with gold before being introduced into the sample chamber. Electron micrographs

were collected using the Jeol 6310 (Jeol, Tokyo, Japan) scanning electron microscope (5 keV).

Powder Compaction and Mechanical Testing

Powder Compressibility

Compressibility was determined as the powder column height reduction on application of an applied load from 0 to 100 kN at a compression rate of 0.17 mm/s.

Powder Compactibility

Compacts, n=8 (6 g, 25 mm diameter) were prepared at a compression rate of 10 mm/min (100 kN, ca. 204 MPa, dwell time 1 minute) using an Instron 1185 (Instron Ltd., High Wycombe, UK) test machine. Diametric compression testing (5 mm/min) was performed 60 minutes after compaction using an Instron 1125 (High Wycombe, UK). Compression and compaction of each set of batches was performed on the same day to reduce the effects of ambient humidity and temperature. The tensile strength of the compacts was calculated from the failure load.[13]

Stress/Strain Relationship

The load/deflection data from the diametric compression test were also converted to stress/strain values.

Statistical Analysis

Minitab (v10, Minitab Corporation) was used for statistical evaluation. One way analysis of variance (ANOVA) followed by Fisher's post hoc test was used to differentiate between samples, where differences were established.

RESULTS

Solid State Nuclear Magnetic Resonance Spectroscopy (SS NMR)

Solid state NMR data of Emcocel HD90 and Prosolv HD90 are shown in Fig. 1. The data in Fig. 1 show that no chemical or polymorphic changes in the novel material were demonstrated by use of this method, when compared to conventional grades of the HD material. Some variation (data not shown) was observed when comparing the ^{13}C SS NMR spectra of

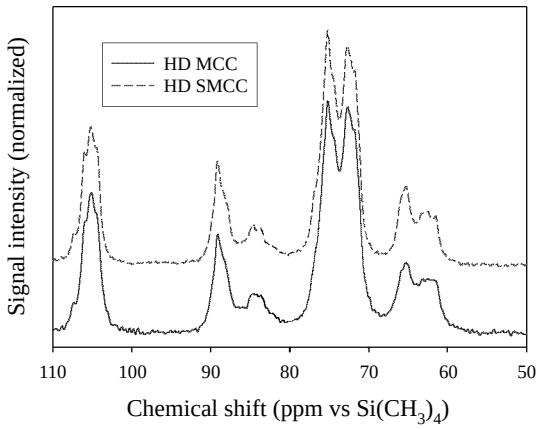

Figure 1. Solid-state ^{13}C NMR spectra of HD SMCC and HD MCC.

HD MCC grades with conventional grades of MCC (e.g., Emcocel 90 M). This is characteristic of the differences between the crystal structure of hardwood- and softwood-derived cellulose fibers and can be used as an aid to identification of materials of unknown provenance.[14]

Other physicochemical characterization procedures such as x-ray diffraction and FT-IR analyses (not shown) did not demonstrate detectable differences.[14]

Scanning Electron Microscopy

Morphologically the particles of silicified material exhibited similar size and shape to images of conventional HD MCC material. Some previous studies have indicated small differences between the morphology of HD SMCC and HD MCC from suppliers other than Penwest. This SEM study (Fig. 2a) suggested that the HD SMCC has a similar morphology to HD MCC and contained agglomerated, approximately spherical particles (Fig. 2b), which is also consistent with HD MCC in this size range. Examination of the particles at higher magnifications suggested that HD SMCC particles contain small aggregates on the surface. These features are consistent with those demonstrated in previous SMCC studies[15] (Table 1).

Surface Area

Micromeritic evaluation of the materials demonstrated that HD MCC has a lower accessible surface area than MCC 90. A lower specific surface area is expected and is likely to explain the higher sensitivity

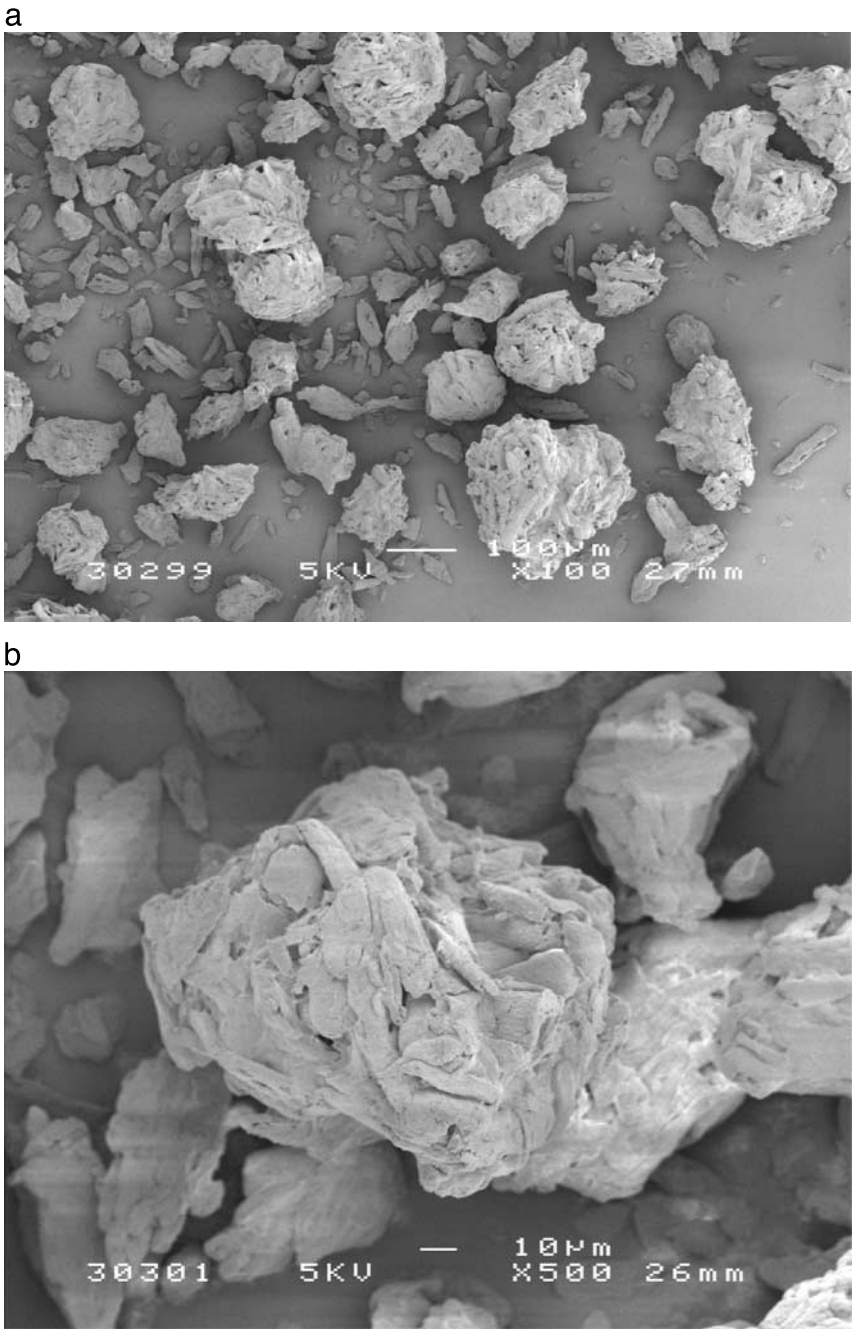

Figure 2. Electron micrographs of HD SMCC: (a) Field photograph demonstrating similarity to conventional HD MCC; (b) Example of HD SMCC particle.

of HD materials to the presence of lubricants at comparable levels.[1] Silicified MCC has a higher surface area, as expected for a material that contains 2% w/w colloidal silicon dioxide, although this is not a direct summation of the values expected for the components. This has been previously demonstrated in related systems.

Particle Size

There were differences in the particle size distributions between the HD grades and regular MCC material. The two HD grades demonstrated similar mean particle sizes, and at the d_{10} range. At the d_{90} range, there were small differences.

Table 1. Physical properties of HD SMCC, HD MCC, and MCC powders.

Material	Density (gcm^{-3})		Carr's index	Particle size (μm)			Surface area (m^2g^{-1})
	Bulk	Tapped		d_{10}	d_{50}	d_{90}	
MCC	0.31	0.40	24	29	110	263	1.25±0.06
				29	109	263	
				29	109	263	
HD MCC	0.46	0.56	19	35	120	287	0.69±0.09
				36	123	292	
				37	120	293	
HD SMCC	0.45	0.54	16	40	124	257	4.32±0.04
				38	123	257	
				38	123	256	

Flow

The flow of the powders was compared by determining their Carr's compressibility index. Basic evaluation of the flow properties of the materials reveals that HD MCC shows slightly improved flowability over the standard grade MCC of similar mean particle size. This improvement in flow, which leads to advantageous properties in tablet die filling and blending, represents one of the key advantages of the ''regular'' HD material.

High density SMCC shows a small, further improvement in flowability, with a lower Carr's index.

Previous work has further demonstrated the improved flow performance of HD SMCC in other tests. While performance in a tableting environment cannot be extrapolated from these tests alone, in limited studies of simple and formulated systems HD SMCC has nevertheless demonstrated improved performance, when measured by tablet weight variation, over conventional HD MCC.[5]

Mechanical Properties

The mechanical evaluation of the materials is detailed in Table 2 and Fig. 3. It can be seen from Table 2 that HD SMCC produces stronger compacts than HD MCC. Moreover, HD SMCC is as compactable as regular MCC using these protocols.

The strength of compacts of HD SMCC is significantly greater than that of compacts of MCC. Additionally, the toughness and ductility of compacts of HD SMCC are greater than those for HD MCC: the toughness is approximately 60% greater in compacts of HD SMCC than HD MCC, which represents a considerable increase in the binding capability of HD SMCC and which may be reflected by a larger ''carrying capacity'' for this material. Indeed, the mechanical properties of compacts of HD SMCC appear to be more comparable to those of regular MCC rather than HD MCC under these compression and testing procedures.

The mechanical properties of compacts of HD SMCC, HD MCC, and MCC are represented in terms of their typical stress/strain characteristics from the diametric test in Fig. 3. It can be seen from these data that compacts of HD SMCC exhibit greater stiffness and ductility than HD MCC. It has previously been reported that these mechanical parameters can be shown to correlate with performance in tableting situations. It would appear that, under these test conditions, silicified MCC has considerably improved mechanical properties compared to HD MCC, and was similar to unmodified MCC.

Table 2. Mechanical properties of compacts of HD SMCC, HD MCC, and MCC.

Material	Tablet density (gcm^{-3})	Tensile strength (MPa)	Deformation (mm)	Toughness (J)
MCC	1.45±0.02	10.1±0.2	0.86±0.02	1.7±0.1
HD MCC	1.46±0.02	7.9±0.2	0.63±0.02	1.0±0.1
HD SMCC	1.46±0.02	10.3±0.4	0.81±0.02	1.6±0.1

204 MPa, n=8. The numbers represent the mean ± standard deviation.

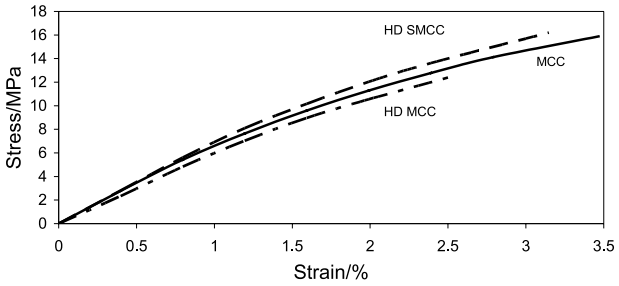

Figure 3. Example of stress-strain data used to generate mechanical properties data.

Previous work has reported that, under model tableting conditions, silicified HD MCC displays considerably improved performance, in terms of tensile strength obtained from a particular compaction force, compared to HD material.[4] In this case also, the silicified HD MCC material exhibited remarkably similar properties to regular MCC.

While the overall benefits in tableting have previously not been attributable to reduced lubricant sensitivity or improved mechanical characteristics, the data here indicate that at least some of this improvement can be attributed to material properties alone.

In further studies it has been reported that the enhanced mechanical rather than flow properties lead to an improved performance in hard gelatin capsule performance, using a tamp filling mechanism, which introduces a lower level of compression on the systems.[6,7]

CONCLUSIONS

Silicified HD MCC, a novel material, appears to show considerable improvement in mechanical properties compared to previously available high density products, while showing no apparent chemical or polymorphic changes. Mechanical deficiencies that have limited the use of HD MCCs in some situations appear to have been overcome for the silicified material.

In addition, the advantageous flow properties of HD MCCs are maintained, leading to improved die filling and blending of the material in direct compression and direct encapsulation procedures.

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REFERENCES

1. Bolhuis, G.K.; Chowhan, Z.K. Materials for direct compression. In *Pharmaceutical Powder Compaction Technology*; Alderborn, G., Nyström, C., Eds.; Marcel Dekker: New York, 1996; 419–500.
2. Nagamoto, S.; Hiroto, M.; Yoshihito, Y. Excipient Having High Compressibility and Process for Preparing the Same. European Patent 0609976, August 10, 1994.
3. Obae, K.; Iijima, H.; Imada, K. Morphological effect of microcrystalline cellulose particles on tablet tensile strength. Int. J. Pharm. **1999**, *182*, 155–164.
4. Cobb, J.; Zeleznik, J.; Montalto, T.; West, L.; Becker, J.; Sherwood, B.E. Compaction characterization of new high density PROSOLV HD. Proc 3rd World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Berlin, April 2000.
5. Cobb, J.; Becker, J.; Lynch, D.; Zeleznik, J. Flow characterisation of a new high density grade of silicified microcrystalline cellulose. Proc 3rd World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Berlin, April 2000.
6. Felton, L.A.; Garcia, D.I.; Farmer, R. Weight and weight uniformity of hard gelatin capsules filled with microcrystalline cellulose and silicified microcrystalline cellulose. Drug Dev. Ind. Pharm. **2002**, *28*, 467–472.
7. Guo, M.T.; Muller, F.X.; Augsburger, L.L. Evaluation of the plug formation process of silicified microcrystalline cellulose. Int. J. Pharm. **2002**, *233*, 99–109.
8. Tobyn, M.J.; McCarthy; Staniforth, J.N.; Edge, S. Physicochemical comparison between microcrystalline cellulose and silicified microcrystalline cellulose. Int. J. Pharm. **1998**, *169*, 183–194.
9. Edge, S.; Steele, D.F.; Chen, A.; Tobyn, M.J.; Staniforth, J.N. The mechanical properties of compacts of microcrystalline cellulose and silicified microcrystalline cellulose. Int. J. Pharm. **2000**, *200*, 67–72.
10. Sherwood, B.E.; Becker, J.W. A new class of high functionality excipients: silicified microcrystalline cellulose. Pharm. Technol. **1998**, *22*, 78–88.

11. Moreton, R.C. Cellulose, silicified microcrystalline. In *Handbook of Pharmaceutical Excipients*, 3rd Ed.; Weller, P., Rowe, R.C., Eds.; Pharmaceutical Press, 2000; 110–111.
12. Carr, R.L., Jr. Evaluating the flow properties of solids. Chem. Eng. January, **1965**, *72* (2), 163–168.
13. Fell, J.T.; Newton, J.M. Determination of tablet strength by diametrical compression test. J. Pharm. Sci. **1972**, *59*, 688–691.
14. Steele, D.F. Amine/microcrystalline cellulose interactions. PhD. thesis; University of Bath, 2002.
15. Edge, S.; Potter, U.J.; Steele, D.F.; Chen, A.; Tobyn, M.J.; Staniforth, J.N. The location of silicon dioxide in silicified microcrystalline cellulose. Pharm. Pharmacol. Commun. **1999**, *5*, 371–376.

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