ELSEVIER International Journal of Pharmaceutics 169 (1998) 183–194

international journal of pharmaceutics

Physicochemical comparison between microcrystalline cellulose and silicified microcrystalline cellulose

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Received 5 January 1998; received in revised form 9 March 1998; accepted 11 March 1998

Abstract

Silicified microcrystalline cellulose (SMCC) has been compared with a standard grade of microcrystalline cellulose (MCC) using several physicochemical techniques in order to elucidate any chemical or polymorphic changes in the material that could be attributed to the silicification process. Samples of SMCC, MCC and dry and wet mixes of MCC and silicon dioxide were analysed using FT-IR, ^{13}C NMR, powder X-ray diffraction, mercury porosimetry, helium pycnometry and scanning electron microscopy together with particle size analysis and deaggregation studies. Analysis of the data obtained from these methods suggested that there were no discernible chemical or polymorphic differences between the samples, indicating that the 'silicification' process produces a material which is chemically and physically very similar to standard MCC. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Microcrystalline cellulose; Silicified microcrystalline cellulose

1. Introduction

Microcrystalline cellulose (MCC) is widely used as a filler and binder for wet granulation, direct compression tableting and as a filler for hard gelatin capsules. It has low chemical reactivity combined with excellent compactibility at low pressures. In a survey carried out by Shangraw and Demarest (1993) relevant workers rated MCC the most useful filler for direct compression tableting.

However, a recent review of the direct compression properties of MCC with respect to its use as a primary excipient nevertheless pointed out a number of limitations to the use of MCC (Bolhuis and Chowhan, 1996), the most important of which were considered to be its low bulk density, high lubricant sensitivity, poor flow characteristics and the influence of moisture on the compression characteristics.

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PII S0378-5173(98)00127-6

In an attempt to reduce some of these problems some manufacturers of MCCs have introduced a number of new grades of MCC which improve some of the properties mentioned above. Most notable amongst these are high density and large particle size grades of the materials, which have been introduced by more than one company. Although these grades may have some advantages in terms of greater plasticity (Muñoz-Ruiz et al., 1994) they form weaker compacts than the base material, which may reflect a reduced surface area for bonding during compression. (Khan and Pilpel, 1986; Zeleznik et al., 1996). In addition, the reduced surface area of large particle size grades makes them more susceptible to the effects of lubricants and they can form poor ordered blends with low particle size drugs (Staniforth and Tralhao, 1996). More recently, a low bulk density grade of microcrystalline cellulose has been produced, with the aim of improving compactibility.

To address some of the functional problems outlined above it has been suggested that coprocessing of MCC with other excipients may improve the performance of materials in direct compression. Included amongst these additives are starch, calcium sulphate (Bavitz and Schwartz, 1974), calcium carbonate (Mehra et al., 1987), dibasic calcium phosphate and β-cyclodextrin. However none of the co-processed materials produced by these methods has found wide commercial use or technical success although cellulose, combined with lactose (Cellactose™), is available commercially (Armstrong et al., 1996; Belda and Mielck, 1996).

Some workers have reported the beneficial properties of surface modification of MCC with silicon dioxide or silicic acid (Nürnberg and Wunderlich, 1995, 1996a,b). This process produces a material with beneficial characteristics with respect to disintegration and mechanical resistance.

A material produced by a process of 'silicification' has recently been described. Electron probe microanalysis of silicified MCC (SMCC) suggests that the process of silicification leads to the deposition of silicon, presumably in the form of silicon dioxide, both on the outer envelope surface of the particle and on exposed surfaces within the particle (Staniforth and Tobyn, 1996). In addition, SMCC has been shown to possess a number of pharmaceutical advantages in terms of powder flow (Khalaf et al., 1997), tablet strength (Sherwood et al., 1996), lubricant sensitivity and wet granulation (Staniforth and Chatrath, 1996). Preliminary data also suggests that the material performs well in direct compression formulations (Riba et al., 1997) and roller compaction (Sheskey et al., 1997).

The aim of this study was to elucidate whether any chemical or polymorphic changes were observable in microcrystalline cellulose following the silicification process.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (Emcocel 90M™) and silicified microcrystalline cellulose (Prosolv SMCC™ 90) were obtained from Penwest Pharmaceuticals, Patterson, NY. Colloidal silica (a 15% w/w aqueous dispersion, Cab-O-Sperse, ex Cabot Corporation, USA), similar to the grade used during the silicification process, was used as a source of silicon dioxide. To prepare silicon dioxide samples a quantity of the colloidal silicon dispersion was tray-dried using a convective oven (Gallenkamp) at 60°C and milled using laboratory mill (type Glen Creston DFH 48).

2.2. Preparation of samples

Samples of MCC and SMCC 90 used throughout this study were used as received. Silicified microcrystalline cellulose SMCC 90 has a 2% w/w silicon dioxide target concentration following silicification.

A 'dry' mix consisting of 10.00 g Emcocel 90 M and 0.20 g dried silica was prepared by trituration in a mortar and pestle; a 'wet' mix was prepared by mixing 10.00 g Emcocel 90 M with

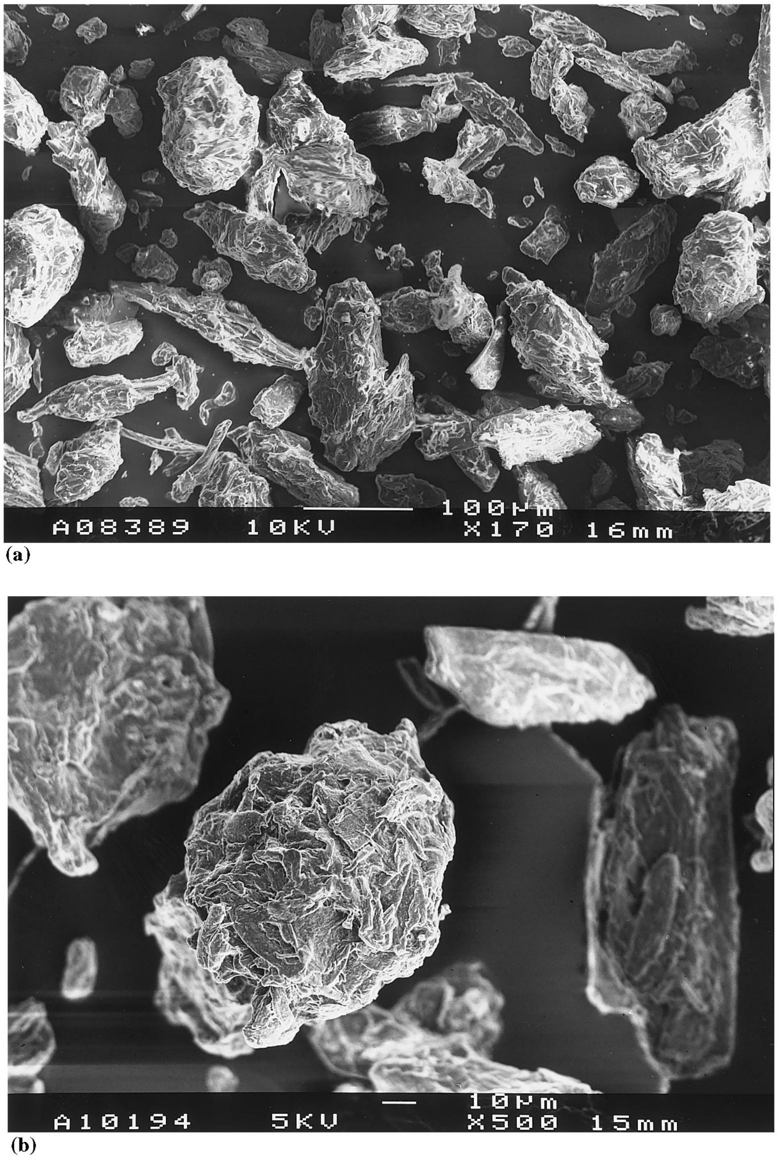

Fig. 1. SEM micrographs of MCC 90.

1.34 g colloidal silica dispersion (equivalent to 0.20 g dry solids) which had previously been diluted in 25 ml distilled water. This latter sample was also tray-dried at 60°C and milled.

2.3. Scanning electron microscopy

Scanning electron microscopy (gold coating, Edwards Sputter Coater, UK) was performed using a Jeol 6310 (Jeol Instruments, Tokyo, Japan) system running at 5–10 KeV.

2.4. Density measurements

True density measurements for the samples were acquired using a helium pycnometer (type Accupyc 1330, Micromeritics, Dunstable, UK). Approximately 3.0 g of the sample powder was

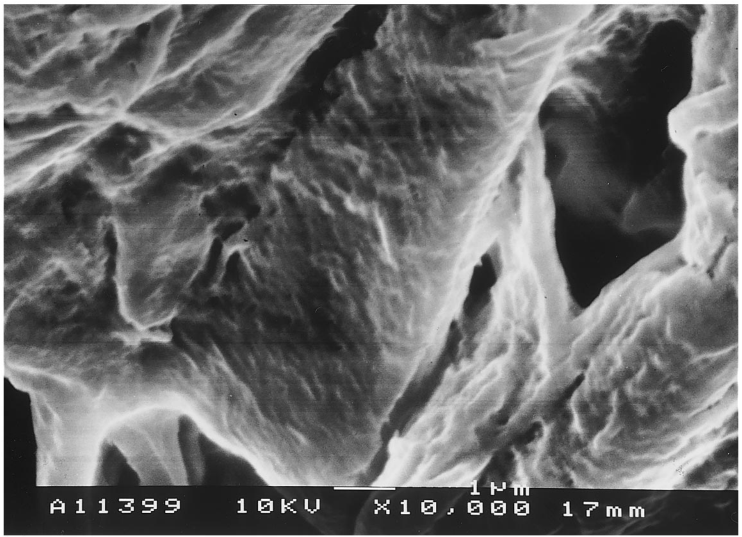

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Fig. 1. (*Continued*)

accurately weighed into a sample cell. The average density for each was determined from ten consecutive measurements within the cell. The results from three runs are reported.

2.5. Particle size

Representative 20 mg samples were prepared by spin riffling into a test tube followed by the removal, at random locations from the bulk of the material, using a sample thief.

Particle size data was obtained using a low-angle laser light scattering (LALLS) system (type Mastersizer X, Malvern Systems, Malvern, UK) equipped with a dry powder feeder. Three separate samples were used to determine a mean particle diameter for each material.

2.6. Deaggregation study

Aerodynamic particle diameters were determined using a laser time-of-flight system (type Aerosizer Mach 2, Amherst Process Instruments, Tewkesbury, UK). The Aerosizer was equipped with the API Aerodisperser device. Samples were analysed over a 300-s period, using a medium shear force as default. Each bulk sample was subjected to five separate determinations, and the average aerodynamic particle diameter was calculated. 'Deagglomeration' was set to 'high', this is equivalent to a pressure drop across the orifice of 5 psi (Hindle and Byron, 1995).

2.7. Porosity measurements

Total intra-particle porosity, pore area and pore size distribution were determined using a mercury porosimeter (type Autopore II, Micromeritics, Dunstable, UK). A representative sample of 0.3–0.5 g was accurately weighed. A penetrometer was selected to ensure that 25–90% of the stem volume was employed during measurement. Mercury intrusion data was collected up to an applied pressure of 7500 psi.

2.8. Attenuated total reflectance Fourier-transform infrared spectra

The surface of each sample was characterized using attenuated total reflectance Fourier transform infrared (ATR-IR) spectroscopy. Spectra were obtained using a Nicolet Magna IR 550 Series II spectrometer (Nicolet Instruments, Warwick, UK) equipped with an ATR cell ('Golden

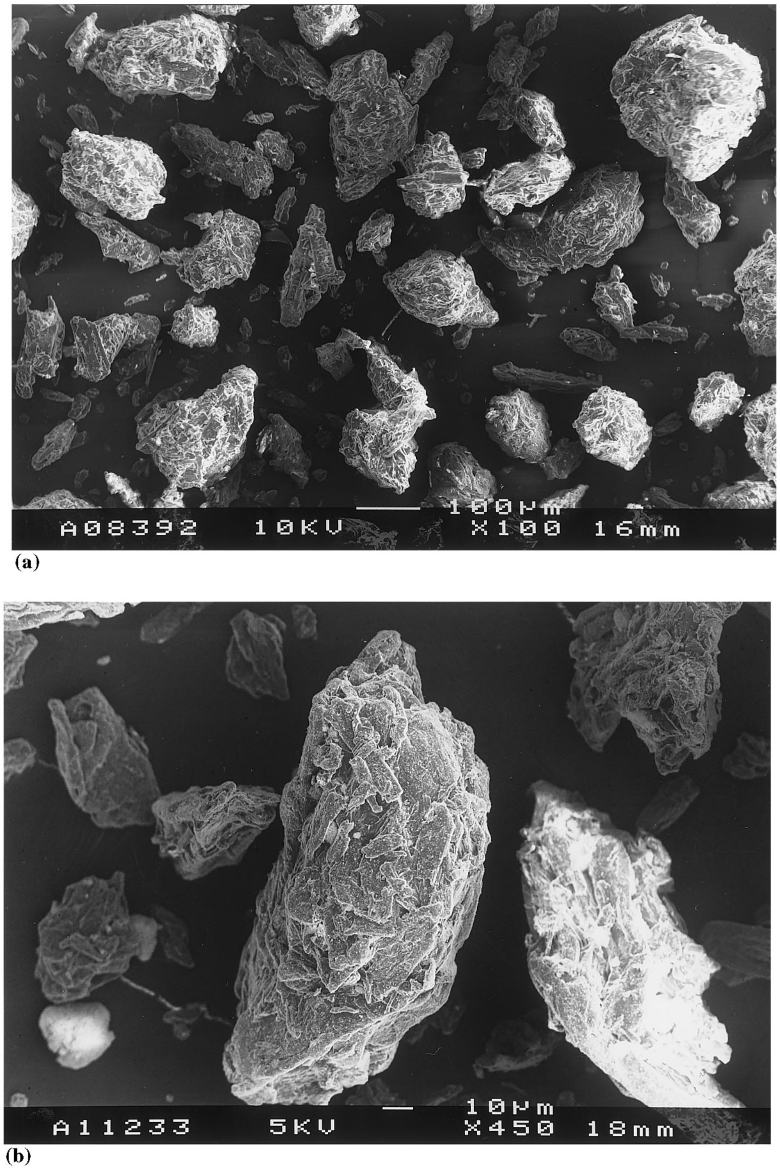

Fig. 2. SEM micrographs of SMCC 90.

Gate' model, Greaseby Specac, Orpington, Kent). Each sample was scanned 64 times at a resolution of 4 cm^{-1} between 4000 and 600 cm^{-1}.

2.9. X-ray powder diffraction studies

Diffraction patterns were obtained using an X-ray powder diffraction system (Phillips X-ray analytical, Cambridge, UK) with the following components: 4 kW X-ray generator (a PW 1730/00); long fine-focus 2 kW copper target X-ray tube (a PW 2273/20), operated at 40 kV and 25 mA; computer-controlled vertical diffractometer goniometer (PW 1820/00); xenon proportional counter (PW 1711/10) with graphite monochromator (PW 1752/00) and automatic divergence slit assembly PW 1368/55); microprocessor diffractometer control (PW 1710/00) and diffraction

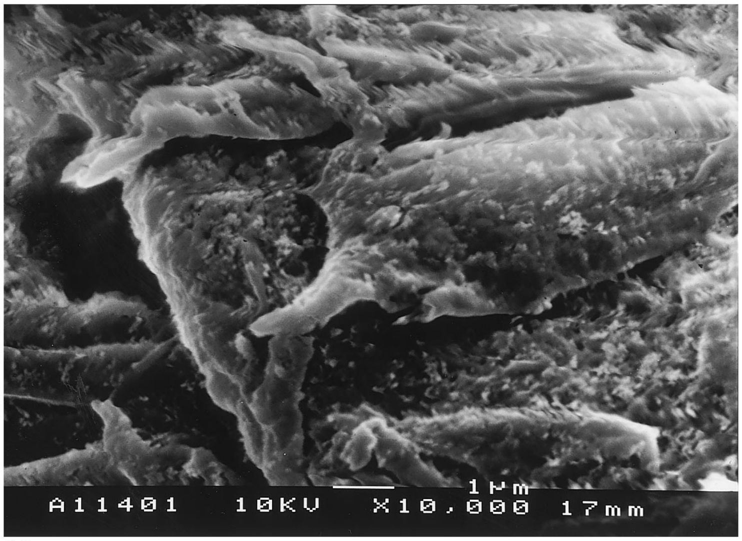

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Fig. 2. (*Continued*)

software (PW 1877 PC-APD, version 3.5b). Each sample was analysed by a single sweep, step size 0.02° (2θ), 13s dwell time. The percentage crystallinity of powder samples was estimated from X-ray diffractograms using the technique of Nelson and O'Connor (1964).

2.10. ^{13}C nuclear magnetic resonance

The Bruker DMX-400 instrument (Bruker Instruments, Coventry, UK) was equipped with a 9.4-T magnet and 4 mm variable temperature probe. A sample (100–150 mg) was packed into a zirconia rotor with a Kel-F end cap, and spun at the magic angle, set using kBr, of 33° with N_2. Spin rates of 2.5–15 KHz with a sample temperature of 298 ± 2 K were used in all measurements. A single-contact cross polarisation pulse sequence was used to acquire all Magic Angle Spinning (MAS) ^{13}C spectra. High-power ^1H decoupling was used throughout. For ^{13}C-^1H cross-polarisation experiments, a contact time of 3 ms was employed, the proton pulse width being calibrated to 3.9 ms. Pre-scan delays of 5–7 s were used and spectral widths were typically 80–140 kHz. Approximately 1024–4096 complex data points were acquired. Carbon chemical shifts were referenced to the high frequency CH_2 peak of adamantane.

Table 1
True density measurements and particle sizes of MCC samples

Sample	Density[a] (g cm^{-3})	Particle equivalent diameters (μm; Malvern Mastersizer)
MCC 90	1.568 ± 0.003	122 ± 2.52
SMCC 90	1.576 ± 0.003	126 ± 2.65
MCC+SiO_2 (Dry mix)	1.576 ± 0.002	105 ± 2.52
MCC+SiO_2 (Wet mix)	1.581 ± 0.001	146 ± 3.06

[a] Determined by helium pycnometry.

Table 2
Aerodynamic particle size as measured by the Aerosizer equipped with an Aerodisperser

Sample	Vol. Average Particle Diam. (μm; Aerosizer)
MCC 90	51.48 ± 0.62
SMCC 90	53.83 ± 2.93
MCC+SiO_2 (Dry mix)	31.10 ± 6.29
MCC+SiO_2 (Wet mix)	24.02 ± 1.13

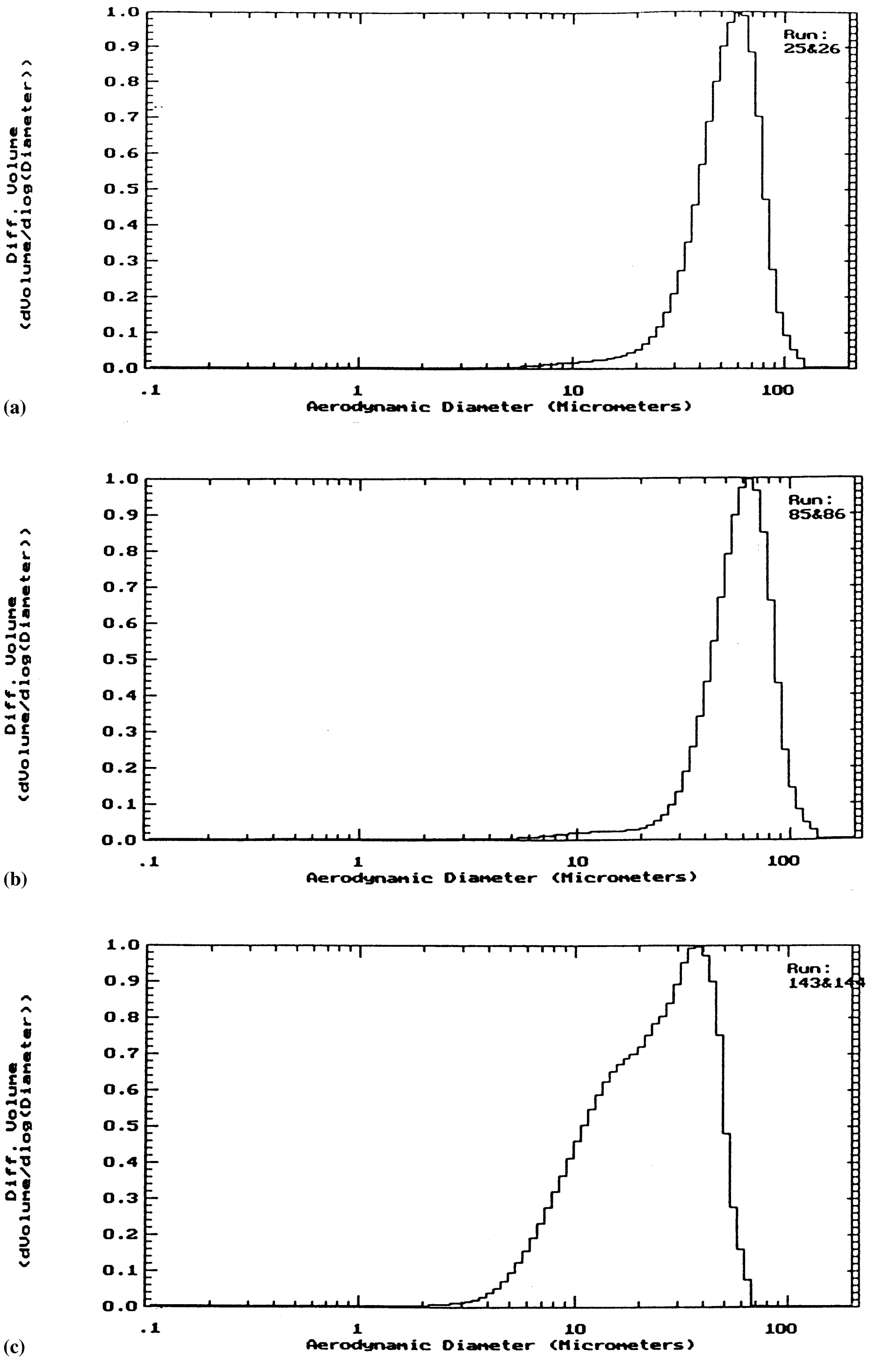

Fig. 3. Aerosizer particle size distributions of MCC (a) SMCC 90 (b) and dry mixed system (c).

Table 3
Porosity data relating to MCC samples

Sample	Total pore area (m^2 g^{-1})	Median pore diam. (μm)	Porosity (%)
MCC	2.12	2.39	30.22
SMCC 90	2.14	2.46	30.15
MCC+SiO_2 (Dry mix)	2.79	2.60	34.28
MCC+SiO_2 (Wet mix)	2.44	2.29	28.65

3. Results

3.1. Scanning electron microscopy

Figs. 1 and 2 show typical images of MCC and SMCC, respectively. At these resolutions no substantial morphological differences between the two samples could be detected, although the surface of the particle in Fig. 2b does appear to contain additional features. However examination of smaller areas of specimen surfaces using high resolution, high definition scanning electron microscopy (Fig. 1c and Fig. 2c) shows distinct differences between the morphological characterisation of MCC in comparison with SMCC. Fig. 2c clearly shows an extensive surface texturisation of SMCC that we conjecture, from the dimensions and shape of these textural features, to be individual or agglomerated colloidal silica particles. Nonetheless, the fact that such textural differences are only apparent in high resolution images leads us to conclude that silicification does not induce gross changes in the shape and texture of microcrystalline cellulose particles.

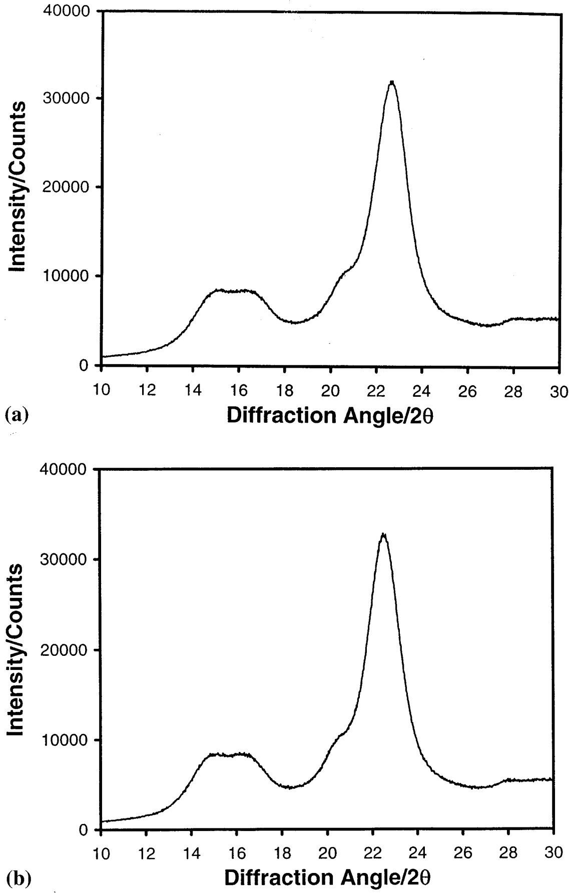

Fig. 4. X-ray diffractograms of MCC (a) and SMCC 90 (b).

3.2. Density measurements and particle size analysis

True density measurements and the average particle diameters for all the samples are displayed in Table 1.

There is little difference between the density measurements of the cellulose samples, with typical values being around 1.57 g/cm^3, which is

Table 4
Percentage crystallinities of cellulose samples equated from X-ray diffractograms

Sample	% Crystallinity
MCC 90	86
SMCC 90	85
MCC+SiO_2 (Dry mix)	85
MCC+SiO_2 (Wet mix)	86

typical of many organic materials and is apparently minimally influenced by the presence of silicon dioxide, whether added by silicification, wet mixing or simply added by blending.

Median equivalent volume diameter determined by LALLS for SMCC was found to be comparable with regular MCC 90 M and within the normal batch to batch variation of such materials. The dry mixed sample does show a reduced particle size. This may be due to attrition during the dry mixing phase of sample manufacture. The possible contribution of deagglomeration to the apparent decrease in particle size is discussed in more detail below. Wet granulation also has an appreciable influence on the observed particle size.

3.3. Deagglomeration study

The Aerosizer, although primarily a particle size analysis equipment, has been demonstrated to be a system capable of deagglomerating particles and particle assemblies (Hindle and Byron, 1995) when used downstream of a so-called Aerodisperser device. The aerodisperser is a high-shear environment in which particles are subjected to a turbulent airstream. It is the exposure of particles to this high shear environment prior to feeding into the Aerosizer that can create some size reduction through de-agglomeration or friabilation of weaker composite materials.

Particle size data obtained using this method were found to be low (Table 2) for the grade of MCC tested, previous measurements (Table 1) and literature results normally giving values consistently above 100 μm. This discrepancy in size analysis data obtained using two different methods was considered to be a sign of the deagglomeration of primary particles of MCC, i.e. defibrillation. Electron microscopy suggests that MCC 90 grade and the equivalently sized Avicel PH102 consist of multiple fibrils each of a similar fundamental size to the 50 μm grade material. Defibrillation of MCC 90 is considered the most likely cause of the reduction in particle size found in Aerosizer analysis. However since the Aerosizer determines particle size by an aerodynamic 'time of flight' system, with particle shape influencing the observed result, this effect may be an instrument dependent phenomenon.

The results for SMCC are very similar to those obtained for the equivalent MCC grade. This was taken as an indication that the silicification process does not influence the particle shape or size, or deagglomeration characteristics of the modified material, when compared with standard grades. By contrast, for the particle size distributions for MCC simply blended with silicon dioxide (Fig. 3c) there is a noticeable downfield shoulder on the particle size distribution, one that is absent from the other two distributions.

This, once again, could be an effect due to attrition in processing. However as a substantial proportion of this shoulder is in the sub-10 μm range, this shoulder could consist of silicon dioxide. This supposition is supported by semi-quantitative X-ray energy dispersible analysis of particle surfaces (Edge et al., 1998).

3.4. Porosity measurements

The values obtained relating to the total pore areas, the median pore diameters and the porosities of the samples are shown in Table 3. These data for MCC 90 and SMCC 90 pore size characteristics were found to be very similar. The similarity in envelope surface area is a reflection of their similar particle sizes, shape and surface textures. It is interesting that there is no apparent increase in accessible surface area with the SMCC 90 sample, whereas there is with dry mixes of silicon dioxide with MCC. Previous studies have demonstrated internal deposition of silicon dioxide in silicified MCC samples (Staniforth and Tobyn, 1996).

3.5. Fourier-transform attenuated total reflectance infrared spectra

It has been demonstrated previously that ATR FT-IR is a powerful technique for the elucidation of structural change in MCC samples, with the ability to predict failure of MCC samples in compression by discovering differences not seen by other physicochemical analyses (Chatrath, 1992).

The ATR-IR spectra of the unmodified microcrystalline cellulose exhibited the following absorption bands: 2870 cm^{-1} (C–H symmetric stretching), 1595 cm^{-1} (O–H symmetric stretch-

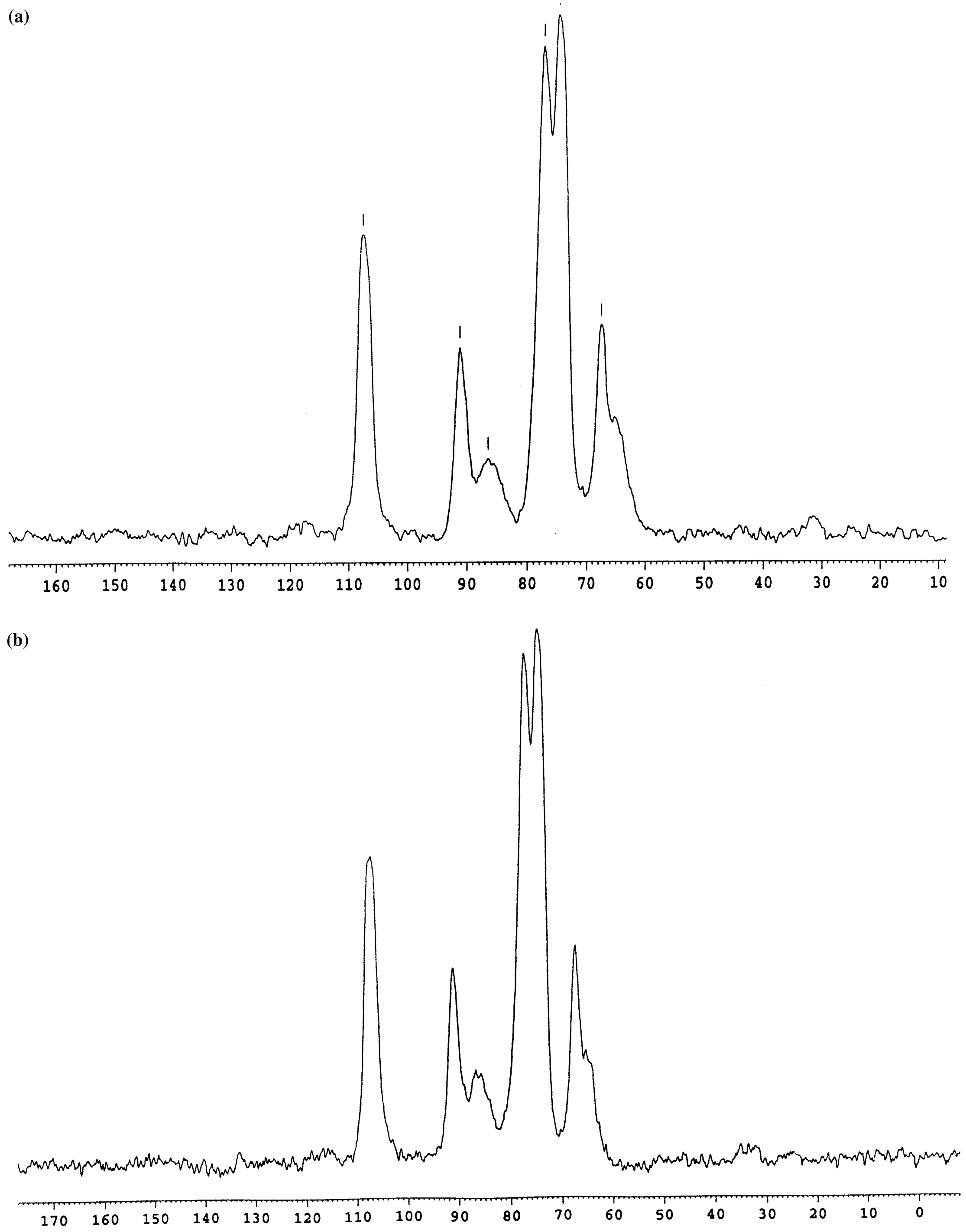

Fig. 5. Solid-state NMR spectra of MCC (a) and SMCC 90 (b).

ing), 1330 cm^{-1} (O–C–O symmetric bending) and four bands between 1200–1000 cm^{-1} (C–C and C–O stretching). The spectrum of silicon dioxide showed a strong band at 1070 cm^{-1} that is typical for silicon-oxygen bonds. The corresponding spectra of SMCC 90, the 'dry' mix of MCC 90 (not shown) with silica and the 'wet' mix of MCC 90 (not shown) with silica were very similar to those that obtained for the pure MCC 90. Any substantial chemical change within the cellulose structure should have resulted in shifts of the bands occurring at 2870, 1070 and 1200–1000 cm^{-1} where hydrogen bonding in samples is apparent. However, no evidence of spectral difference in these regions was found with the modified samples, whether following silicification or blending. It would appear that the silicification process does not cause gross changes in the chemical bonding within the structure, and that the physical processes (dry blending and wet granulation) also appear to have little influence. The lack of substantial differences between the silicified and standard materials is further supported by subtractions of spectra, where the spectra for the modified materials were taken away from that of the base MCC material. These showed very small differences due to the physical presence of silicon dioxide, confirming its presence in the SMCC sample, but a flat baseline in all other relevant areas.

3.6. X-ray diffraction studies

Several previous studies have shown that the crystallinity of MCC samples from different commercial sources can be variable (Soltys et al., 1984; Rowe et al., 1994) and that such changes may result in different functional performance. Furthermore the presence of the polymorphic form of cellulose II in the sample can be shown to have substantial deleterious effects on the functionality of the material (Chatrath, 1992; Landin et al., 1993).

The X-ray diffractograms relating to the MCC samples are shown in Fig. 4. The percentage of crystalline material was estimated from the data according to a relationship described by Nelson and O'Connor (1964) and are shown in Table 4. The diffractograms clearly show that the cellulose is present in the form of cellulose I and not cellulose II (shown by the absence of the doublet in the main peak intensity), and all are in contrast to the diffractogram of amorphous cellulose. There are no significant differences between any of the samples tested, once again demonstrating that there are no gross physical or chemical changes induced by silicification.

3.7. ^{13}C nuclear magnetic resonance

This technique was employed to confirm the findings from ATR-IR and X-ray diffraction as any chemical shift for a particular carbon within the cellulose is evidence of differing bond angles or differing degrees of bonding. The spectra obtained are shown in Fig. 5. In the case of MCC 90, the presence of a sharp peak at 91 ppm, corresponding to C_4, is evidence of high degrees of crystallinity and confirm the data obtained by X-ray diffraction. The peak occurring at 67 ppm corresponds to C_6 and is indicative of the cellulose being present as cellulose I (again confirming X-ray diffraction). The shoulder associated with this peak, at 64 ppm, may be evidence of amorphous material. The ^{13}C NMR spectra for all of the samples are very similar, indicating that no substantial polymorphic or chemical changes are apparent in the modified materials.

4. Conclusion

Thus, in conclusion, it is evident from these characterisation techniques that when microcrystalline cellulose is silicified in the preparation of SMCC 90, no bulk chemical change in the MCC is observed at the resolutions tested and no observable polymorphic changes are induced.

The fundamental chemical properties of the novel material are very similar to those of the parent material. Thus the improved functionality of SMCC 90, in terms of improved bulk physical properties and mechanical characteristics, is considered to be due to some other intrinsic property rather than as a change in the base chemical parameters of the novel material.

Acknowledgements

We are grateful to Penwest Pharmaceuticals for the support of this project (G.P. McCarthy, M.J. Tobyn, S. Edge). We thank Barry Chapman for help in XRD studies and Louise Kelly for aiding with porosimetry. The helpful comments of Andy Thompson in analysing the solid state ^{13}C NMR results are appreciated.

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