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Water sorption and near IR spectroscopy to study the differences between microcrystalline cellulose and silicified microcrystalline cellulose before and after wet granulation

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Abstract

Silicified microcrystalline cellulose (SMCC) has been shown to have advantages over conventional microcrystalline cellulose (MCC). These advantages are (i) improved tablet strength compared to that achieved with MCC, (ii) the retention of compressibility after wet granulation, whereas MCC produces weaker tablets after wet granulation, and (iii) superior flow properties than MCC. In this study gravimetric and calorimetric vapour sorption data and near IR spectroscopy have been used to study MCC and SMCC before and after wet granulation. It was found that MCC, SMCC and wet granulated SMCC had essentially identical physical structures (except for a size increase due to granulation). Wet granulated MCC had a different enthalpy of water sorption at low RH, and its near IR spectrum was different from the other samples in the region which relates to C–H bonding. It can be concluded that MCC and SMCC are of very similar structures, thus these analytical techniques cannot provide an explanation for the improvements in compressibility. However the change in compressibility in MCC after wet granulation may relate to the observed differences in internal bonding in this sample. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Microcrystalline cellulose; Silicified microcrystalline cellulose; Water sorption; Isothermal microcalorimetry; Near IR; Swelling; Absorption

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1. Introduction

Microcrystalline cellulose (MCC) is used as a compression aid in directly compressed tablet for-

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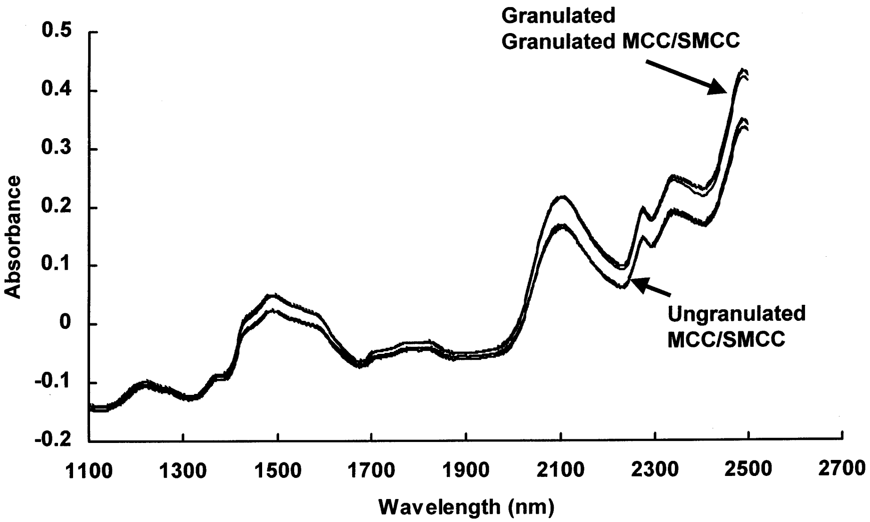

Fig. 1. NIR spectra for MCC and SMCC before and after wet granulation, showing the similarity between the four samples and the displacement to higher absorbance levels for the granulated materials, due to an increase in particle size.

mulations and as a diluent in wet granulated products. Bolhuis and Chowhan (1996) have highlighted some problems with microcrystalline cellulose, which include the fact that the compression properties deteriorate after wet granulation. Silicified microcrystalline cellulose (SMCC) (marketed as Prosolv SMCC by Penwest Pharmaceuticals) has been claimed to be more resistant than conventional MCC to the effects of granulation, i.e. to retain compaction properties after wetting and drying. Sherwood and Becker (1998) showed that tablets made of wet granulated MCC had much lower tensile strength than tablets made from MCC before granulation. Wet granulated SMCC had the same tensile strength as the original MCC at all compression forces studied. Sherwood and Becker (1998) also showed that physical mixtures of MCC and colloidal silica did not achieve the same protection as SMCC, against loss of tensile strength. The observation that SMCC yields tablets of higher tensile strength than MCC at any selected compression force and the existence of improved flow properties for SMCC were also reported by Sherwood and Becker (1998).

Despite the changes in performance during tabletting operations, it has proved difficult to find analytical tests which differentiate between MCC, SMCC and the same materials after moistening and drying (wet granulation). Tobyn et al. (1998) have studied the physico-chemical properties of MCC and SMCC using FT–IR, ^{13}C NMR, powder X-ray diffraction, mercury porosimetry, helium pycnometry and scanning electron microscopy. Using these techniques they were unable to find any chemical or polymorphic differences between MCC and SMCC. There is a clear need to find tests to differentiate between MCC based samples which have different functionality.

Near-infrared spectroscopy is a technique which yields both physical and chemical information about products. NIR has been used to investigate polymorphism (Aldridge et al., 1996), moisture in lyophilised products (Kamat et al., 1989) and crystallisation of amorphous lactose (Buckton et al., 1998). As the technique seems valuable to study changes in physical form and the sorption of water it has been used here to study the microcrystalline cellulose samples. The aim of this study was to use near-infrared (NIR) spectroscopy, gravimetric and calorimetric water sorption, to identify any structural differences between MCC and SMCC, both before and after granulation. The structures of the samples are thus being tested by a spectroscopic method and a

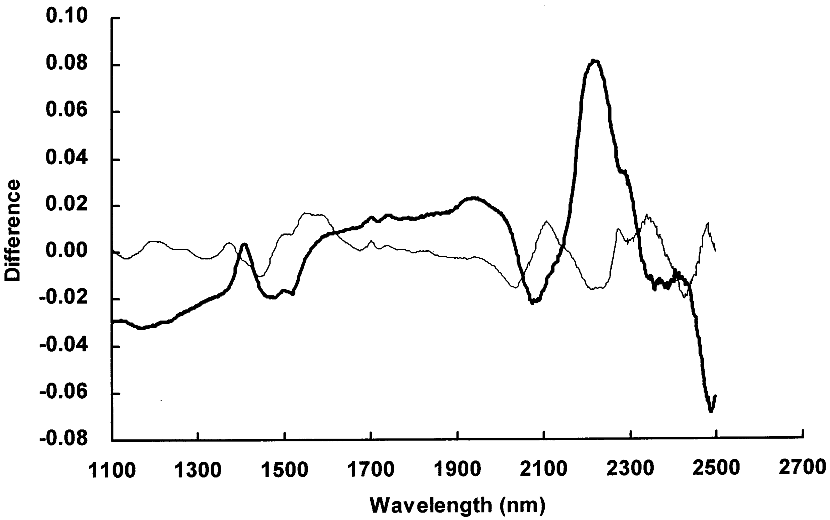

Fig. 2. The difference between the normalised spectra for granulated and original MCC (thin line) and SMCC (bold line).

molecular probe (water vapour), both of which are able to yield information on the physical form of the materials.

2. Materials and methods

Microcrystalline cellulose (Emcocel 50M), silicified microcrystalline cellulose (SMCC 50M), and the wet granulated versions of these products were all obtained from Penwest Pharmaceuticals, Patterson, NY, USA. The wet granulated materials were as described by Sherwood and Becker (1998). The powders had simply been moistened in a 10 l Baker–Perkins high shear mixer-granulator for 3 min with sufficient water added to equate to 42% of the wet mass (this being thought to cause the maximum loss of tensile strength of subsequent compacts, Chatrath, 1992). The wet mass was passed through a 12-mesh screen and tray dried for ca. 3 h to a moisture content of 5%. To minimise the size differences the granules were sieved and a range between 74 and 177 μm was collected and used. Both MCC and SMCC were exposed to exactly the same process. No other excipients were added during granulation. The granulation step was performed at Penwest Pharmaceuticals.

Blank experiments were used to select glass containers which had the same background near-infrared diffuse reflectance spectra. Whilst NIR does not detect silica it was still found that some bottles did yield strong peaks in their NIR spectra, which we assume to be due to impurities in the glass, these bottles were not used in the study (Yoon et al., 1998). Those bottles which were selected were loaded with 2 g of dry powder and a tube containing either a desiccant or a saturated salt solution. The bottles were sealed and stored in an oven at 20°C. The dry powders, and samples stored with salt solutions at controlled humidities of 12, 23, 33 and 75% RH, were placed periodically on the sample stage of a rapid content analyser module attached to a Foss NIRSystems 6500 spectrometer. Each NIR measurement was the mean of 32 scans obtained for each sample, over the wavelength range 1100–2500 nm. The process was repeated six times.

2.1. Gravimetric and calorimetric sorption studies

The water sorption isotherms of MCC, SMCC and the two wet granulated samples were measured gravimetrically (using a Dynamic Vapour Sorption apparatus, Surface Measurement Systems) and calorimetrically (Thermal Activity

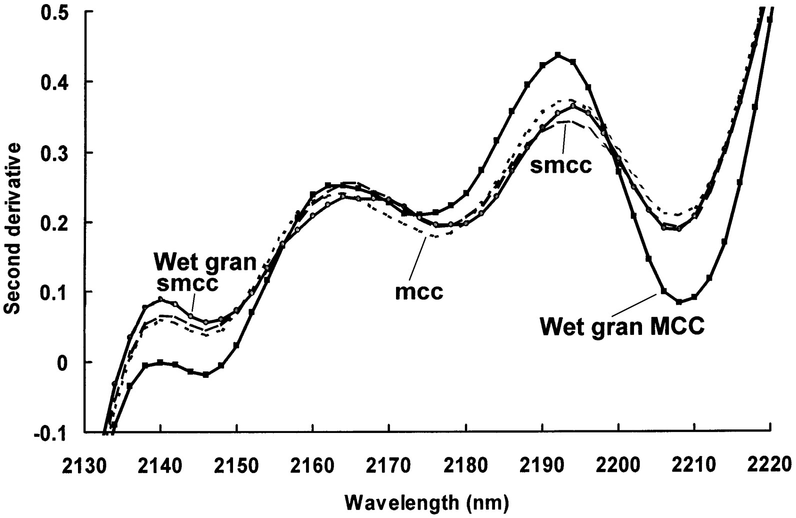

Fig. 3. The second derivative spectra in the region 2130–2220 nm, showing similarities for MCC, SMCC and wet granulated SMCC, but a different response for wet granulated MCC.

Monitor, Thermometric Ltd. using an RH perfusion cell, with a dry nitrogen supply and a mass flow controller). All sorption data were obtained by starting at 0% RH and then increasing in 15% RH steps until 90% RH, at 25°C[2]. The gravimetric water uptake was expressed as moles of water sorbed per gram of cellulose, and the calorimetric data as Joules per gram of cellulose. Subsequently, these two data sets were combined to allow the enthalpy of sorption to be expressed in units of Joules per gram of sorbed water. This approach allows a comparison to be made between the powders, by using water vapour as a molecular probe of the structure (especially the amorphous regions, which is where the absorption occurs).

3. Results and discussion

3.1. NIR study on the dry samples

The NIR spectra for the four dry samples are shown in Fig. 1. It can be seen that the two powders (MCC and SMCC) have lower absorbance values than the two wet granulated samples across the entire spectra. This is due to the increase in particle size as a consequence of granulation, even though a sieved fraction was used. It is a valuable aspect of NIR spectroscopy that the physical form of the material is monitored at the same time as the chemical nature. The standard normal variate (SNV) of the spectra diminishes the contribution from physical effects resulting in the four spectra appearing to be almost superimposed (not shown), and allows the underlying differences in the materials to be investigated. SNV and other normalisation techniques for NIR spectra have been discussed by Blanco et al. (1998).

The first attempt to probe any differences which were a consequence of granulation was to subtract the normalised spectra for the original powder from that for the granulated material. This was performed for the MCC and the SMCC samples and the difference spectra are shown in Fig. 2. The major difference between the samples was in the region above 2100 nm for the wet granulated MCC material. In Fig. 3, the second derivative plots of this region of the spectra are shown. The advantages of using the second derivative are that the baseline is flattened and the

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[2] The sorption data have been presented on a poster at the 1997 AAPS conference, however, the data were not included in the short published abstract (Buckton and Darcy, 1997).

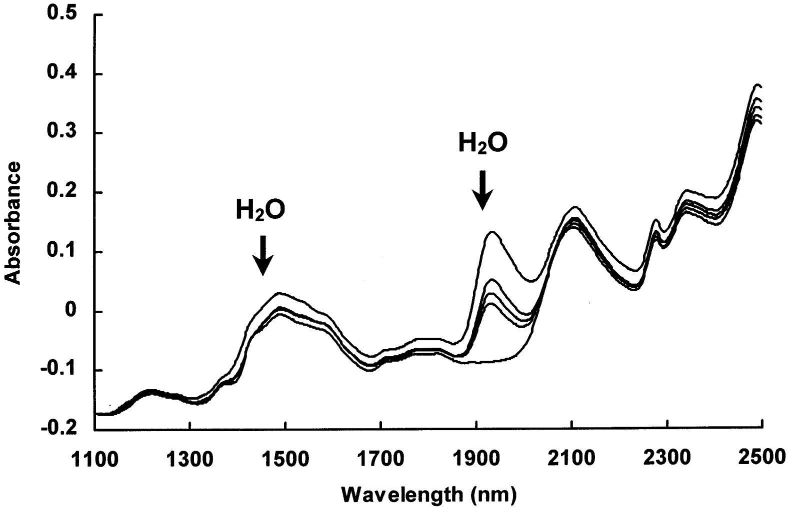

Fig. 4. NIR spectra for MCC after sealing into glass jars either dry (0% RH) or with salt solutions giving equilibration to 12, 23, 33 and 75% RH (at 20°C). (Bottom trace, 0% RH, followed by 12, 23, 33 and top trace, 75% RH)

peaks are given greater intensity. The first derivative of a conventional spectroscopic peak gives the rate of change, thus the up slope and down slope of the original peak would convert to a positive and negative peak respectively (with the zero point being at the wavelength of the original peak maximum). When using second derivative (which is the rate of change of the first derivative plot) an initial positive peak is seen, followed by a substantial negative peak then a further small positive peak. The minimum of the negative peak is the area of interest as this is related to the wavelength of the maximum on the original spectrum. It can be seen (Fig. 3) that three of the materials are identical, but that the wet granulated MCC has different strength peaks at 2146, 2174 and 2208 nm, which are slightly displaced in wavelength. It is difficult to get an exact structural identification for these peaks, however, 2100 nm has been assigned as an O–H stretch and a C–O–O stretch third overtone (Shenk et al., 1992; Osborne et al., 1993). This would indicate that the peak at 2146 nm is associated with internal hydrogen bonding. The 2364 nm peak is the region of C–H stretch and C–H deformation combinations (reported to be at 2336 nm for cellulose by Shenk et al., 1992; Osborne et al., 1993). The changes at both 2146 and 2208 nm for wet granulated MCC indicate a change in both internal H-bonding and C–H-bonding for this sample which is not observed when SMCC is wet granulated.

3.2. *The humidified samples (NIR and enthalpy of sorption)*

A series of NIR spectra for a sample of MCC is shown in Fig. 4, as a function of RH (following storage for 30 days with the saturated salt solution). The major differences seen are that a substantial peak is observed at 1940 nm, which is due to the absorbed water, also there is a baseline displacement. The baseline shift is due to the change in particle size, which is a consequence of swelling of the sample in the water vapour.

The extent of water sorption to each of the four samples proved to be identical within experimental error (Table 1), however, the enthalpy of sorption for wet granulated MCC proved to be different to that for MCC, SMCC and wet granulated SMCC. The enthalpy of sorption data are presented in Table 2, and each data point is the enthalpy change associated with the change between the two humidities (i.e. the data are non cumulative). The total heat changes are small which may indicate that more than one process occurs simultaneously. Thus for example, the ex-

Table 1
Weight of water sorbed by cellulose samples at 25°C, expressed as % w/w increase (S.D.) $n = 5$

RH (%)	MCC	SMCC	Wet gran. MCC	Wet gran. SMCC
15	2.7 (0.02)	2.8 (0.02)	2.8 (0.03)	2.7 (0.01)
30	3.9 (0.01)	4.0 (0.01)	3.4 (0.03)	4.0 (0.04)
45	4.9 (0.01)	5.0 (0.01)	5.2 (0.04)	5.2 (0.04)
60	6.3 (0.02)	6.3 (0.01)	6.3 (0.30)	6.5 (0.06)
75	8.5 ((0.03)	8.6 (0.02)	8.5 (0.43)	8.5 (0.08)
90	12.4 (0.09)	12.7 (0.05)	12.5 (0.13)	12.5 (0.12)

pected large exotherm for water absorption may be partially masked by an endothermic process within the cellulose. There was no significant difference between the enthalpy of water sorption for MCC and SMCC. Also there was no significant difference between MCC and wet granulated SMCC, or between SMCC and wet granulated SMCC (*t*-tests, $p = 0.05$). This indicates that the amorphous cellulose structure is essentially the same for each of these three samples. There was a significant difference between MCC and wet granulated MCC at the 15–30 and 30–45% RH steps. The different energetics of water sorption to the wet granulated MCC (Table 2) show that the environment into which the water absorbed was different, and thus the amorphous cellulose had repacked in some way. This is in keeping with the NIR spectroscopy studies, where it was noted that the wet granulated MCC had a change in the C–H-bonding.

The difference in enthalpy of sorption for the wet granulated MCC could either be caused by the fact that this sample is physically different to the other three (thus making water sorption energetically different), or that the exposure to humidity causes a change in the sample which would contribute to the calorimetric response. The NIR spectra that were collected for each of the four samples did not indicate any change in internal bonding as a consequence of storage at different humidities. For example close examination of the traces in Fig. 4, and similar spectra for the other three sample (not shown) did not reveal any changes in the C–H bonding region during water sorption.

It can be concluded that the change in structure in the wet granulated MCC came about as a function of the wet granulation and drying of MCC, rather than being a change that was induced during water sorption. This change of internal bonding within the cellulose, produced an altered physical structure, which resulted in the change in the enthalpy of sorption of water in the cellulose. The different data sets give two means of investigating the cellulose structure, these being the NIR spectra and the use of water molecules as molecular probes. Both approaches show that the MCC and SMCC do not have different structures in the cellulose, but that the SMCC is able to retain its structure after wet granulation, whereas the MCC is not.

Table 2
Enthalpy of water sorption (J/g of water)

RH change (%)	MCC	SMCC	Wet gran. MCC	Wet gran. SMCC
0–15	3.02	2.58	2.57	2.51
15–30	2.83	2.89	6.28	2.73
30–45	2.97	2.93	1.79	2.46
45–60	2.41	2.36	3.02	2.58
60–75	2.33	2.19	2.07	2.19
75–90	2.23	2.10	2.01	2.02

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