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Production and evaluation of size reduced grades of microcrystalline cellulose

S.R. Levis, P.B. Deasy *

Department of Pharmaceutics, School of Pharmacy, University of Dublin, Trinity College, Dublin 2, Ireland

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Abstract

Size reduction of microcrystalline cellulose (MCC, Avicel® PH-101) powder by ball milling was poorly effective, particularly in the presence of sodium lauryl sulphate (SLS), which tended to form a protective foam. Ultrasonic homogenisation of an aqueous suspension more readily produced ultra-fine MCC, even in the presence of the surfactant and two other de-aggregating agents, and factorial experimentation was used to optimise the process. The product was recovered by spray-drying and readily redispersed in water without re-aggregation. Two new grades of ultra-fine MCC, prepared by an optimised treatment with or without 1% SLS, were characterised by a range of techniques in comparison to the starting coarser grade, Avicel® PH-101. Mercury porosimetry and scanning electron microscopy confirmed the less porous and smaller particle size of the new grades, where deposition of SLS as a coating was evident. Surface area determination confirmed that the size-reduced grades had larger specific surface areas, particularly the SLS treated material. Low temperature DSC and X-ray diffraction studies suggested that the new ultra-fine grades were more amorphous. Collectively the results indicate that the new grades should have unique functionality, possibly of benefit in pharmaceutical formulation. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Microcrystalline cellulose; Ultra-fine grades; Ultrasonic homogenisation; Sodium lauryl sulphate; Characterisation

1. Introduction

Microcrystalline cellulose (MCC) is prepared from native cellulose by controlled acid hydrolysis, which preferentially attacks amorphous regions, followed by back-neutralisation with alkali prior to recovery by spray-drying. The material produced is composed largely of aggregated bundles of crystallites of cellulose formed as porous particles, the various grades of which can be influenced by the source of the wood pulp used, the severity of the processing employed, co-processing with other additives such as sodium carboxymethylcellulose, and both the particle size range and residual moisture content as affected by the spray-drying conditions employed. Avicel® PH-101 (FMC) is among the most widely used pharmaceutical grades, has an average particle size of 50 μm approx, and is employed mainly as a filler/disintegrant/binder in tablets and capsules,

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* Corresponding author. Tel.: + 353-1-6082784; fax: + 353-1-6082783.

E-mail address: pdeasy@tcd.ie (P.B. Deasy).

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and as an aid in extrusion/spheronization. Attempts to size reduce this and other grades by mechanical and other means are resisted by strong hydrogen bonding associated with surface groupings, which also promote re-aggregation during drying procedures.

Recently Deasy and Law (1997) reported that sodium lauryl sulphate (SLS) surprisingly reduced drug release from spheronised pellets containing indomethacin, and Avicel® PH-101, when the wetting agent was added to the mix. This effect was ascribed to a possible de-aggregatory effect of the SLS on the MCC, favouring the formation of a more effective retardant matrix. This project aims to extend that work by optimising the formation of a surfactant aided de-aggregated grade of MCC and by examining a range of physical processes for achieving the desired size reduction, so as to produce new grades with possible unique functions.

2. Materials and methods

2.1. Materials

Citric acid monohydrate, di-sodium hydrogen phosphate dodecahydrate (Riedel de Haen), helium, nitrogen (Air Products), microcrystalline cellulose (MCC) (Avicel® PH-101, FMC), sodium citrate (SC), sodium hexametaphosphate (SH) (Aldrich), sodium lauryl sulphate (SLS) (Sigma) and water [HPLC grade (Rathburn) and glass distilled] were used. All reagents were GPR unless otherwise indicated.

2.2. Preparation of size reduced grades of MCC

Avicel® PH-101 was dispersed in water as a 3% suspension, with or without added 0.15% SLS, and size reduced by wet grinding in a vibratory ball-mill (Retsch) at 60 or 80 Hz for 5 or 10 min. Avicel® PH-101, with or without added SLS 0.25 or 0.5% to the aqueous 5 or 10% suspensions respectively, was size reduced also by multiple passes through an ultrasonic homogeniser (Minisonic, Ultrasonics Ltd). Size reduced material was recovered as a powder by spray-drying (Buchi 190) the continuously agitated slurry, using optimised settings of delivery rate at 5–10 ml/min, air flow rate at 600 NI.h and inlet temperature at 125°C.

2.3. Particle size analysis by laser diffraction

Samples of the various grades of MCC produced were examined for particle size by dry-powder or powder-in-liquid techniques using a laser diffraction particle size analyser (Malvern 2600c), with a 300 mm lens attached, which is capable of measuring particles in the size range 5.8–564 μm.

2.4. Mercury porosimetry

The porous structure of grades of MCC was determined by mercury porosimetry using a Pore-Sizer 9320 system (Micromeritics). Measurements were done on powder samples using a 3 cm^3 'powder sample' penetrometer (sample weight 350 mg). Samples were dried to constant weight using a vacuum oven set at 80°C and removed just prior to analysis. Intrusion pressures between 0.5 and 30 000 psi were used, corresponding to pore diameters between 360 and 0.006 μm. The low pressure analysis (0.5 to ~20 psi) was done semi-automatically and the high pressure analysis was automatically controlled, both using the equilibrium mode with a time interval of 10 s.

The technique can be used to estimate the surface area of samples.

2.5. Scanning electron microscopy (SEM) studies on powders

Samples from batches of powders were mounted on aluminium stubs using double-sided sticky tape, vacuum coated with gold film (Polaron SC 500) and examined using a scanning electron microscope (LEO Stereoscan S-360) for surface morphology.

2.6. Surface area

Surface area of grades of MCC was determined also by a nitrogen adsorption technique using a Micromeritics Gemini 2370 Surface Area Analyser. Moisture was removed from the samples prior to the surface area measurement by placing them in a vacuum oven for 24 h at 70°C at a pressure of 500 mbar. Subsequently, samples were degassed using a Micromeritics FlowPrep 060 Degasser. The FlowPrep uses a flowing gas (helium), which is passed over a heated sample (70°C) to remove moisture and other contaminants.

2.7. Differential scanning calorimetry (DSC)

Microcrystalline cellulose sample batches (Avicel® PH-101, Grade X and Grade Y) of various hydration levels were prepared by adding a pre-determined weight of HPLC grade water to 5 g approx. of the microcrystalline cellulose grade in sealed glass bottles. The contents of bottles were periodically agitated and allowed to equilibrate for at least 1 week. Following this equilibration step, 6–8 mg approx. of the hydrated cellulose samples was accurately weighed out and transferred to dry aluminium DSC pans and sealed hermetically. The hermetically sealed pans were left for a further period of time (1–2 weeks approx.) before testing to facilitate re-equilibration after transfer from the sample bottle. DSC studies were performed using a Perkin–Elmer DSC 7 calorimeter equipped with a thermal analysis station. The instrument was calibrated by standard procedures. An empty aluminium pan was used as reference. DSC traces were recorded at a fixed scanning rate of 10 K/min for both the cooling and heating cycles. Endotherms were obtained from the cooling cycle performed within the temperature range of 25°C to -60°C, while exotherms were obtained from the heating cycle performed in the reverse temperature range.

Following DSC analysis, each pan was removed, weighed to determine if any weight loss had occurred (which would have indicated an incorrectly sealed pan), pierced and then dried in an oven set at 60°C to constant weight to determine the actual water content.

2.8. X-ray diffraction analysis

X-ray diffraction patterns were obtained for the various grades of MCC using a Siemens D500 X-ray powder diffractometer. Powdered samples were studied by placing a thin layer of the powder in conventional cavity mounts. The samples were scanned from 5–40° 2θ. A 1.00° dispersion slit, a 1.00° anti-scatter slit, and a 0.15° receiving slit were used. The Cu anode X-ray was operated at 40 kV and 20 mA in combination with a Ni filter to give monochromatic Cu Kα X-rays ($\lambda = 1.5418$ Å).

3. Results and discussion

3.1. Mechanical size reduction of Avicel®-PH101 by wet grinding

The results of wet grinding on particle size reduction at two vibratory frequencies, two grinding times and in the presence or absence of SLS are shown in Table 1. In all cases modest size reduction compared to the control occurred, particularly after increasing time of treatment. Particle size histograms showed a progressive conversion of the mono-modal MCC control to a bimodal size distribution, indicative of fracture of smaller crystallites from larger bundles. The pres-

Table 1
Median particle size of wet ground samples of MCC compared to untreated control

Grinding frequency (Hz)	Grinding time (min)	SLS content (%)	Particle size (µm)
–	–	–	56.4
60	5	–	39.0
60	10	–	30.2
80	10	–	27.9
60	10	0.15	45.0

Table 2
Median particle size of MCC size reduced by ultrasonic homogenisation

MCC conc (%)	Homogenisation cycles	SLS conc (%)	Particle size (μm)
5	1	–	28.4
5	2	–	20.7
5	5	–	15.5
5	10	–	13.1
5	25	–	11.0
5	10	0.25	14.3
10	5	–	15.3
10	10	–	13.0
10	2	0.5	20.2

ence of SLS appeared to protect against size reduction by forming a foam with air, which cushioned the MCC particles from the fragmentary effect of the ball milling. However, because the process was not considered energy efficient and was capable of producing only small quantities of poorly size reduced material, another mechanical method suitable for easy incorporation as a prior step to spray-drying in the commercial manufacture of MCC was examined.

3.2. Mechanical size reduction of Avicel®-PH101 by ultrasonic homogenisation

Müller and Peters, 1998 reported the successful use of high-pressure homogenisation to form ultra-fine drug suspensions. In this project, a similar approach in preliminary experiments was applied to aqueous suspensions (5 and 10%) of MCC, employing increasing numbers of passes through the available homogeniser. The results of particle size analysis in the wet state as shown in Table 2 indicate significant size reduction was obtained, where the concentration of solids in the feed suspension had little effect but increasing numbers of passes through the homogeniser, particularly up to 5, was very efficient at promoting size reduction towards a bimodal distribution. Whereas incorporation of SLS did not improve size reduction in the wet state, it might prevent re-aggregation and aid re-dispersal of the spray-dried product in aqueous media. Unlike the wet grinding technique, large quantities of MCC suspension could be rapidly and easily milled to a finer particle size range by the technique as a prior step to recovery by spray-drying as a powder.

3.3. Optimisation of the size reduction by ultrasonic homogenisation

Factorial experimentation (2^3 with duplication) was used to optimise the size reduction of MCC by ultrasonic homogenisation using 2 levels of the three factors SLS concentration (0 or 1% — A), homogenisation cycles (1 or 5 — B) and suspension concentration (5 or 10% — C). The main effects and interactions calculated are illustrated graphically in Fig. 1.

The results indicate that each of three factors have a statistically important effect on the size reduction of MCC in the wet state by ultrasonic homogenisation, with the number of homogenisation cycles employed being the most influential. The presence of SLS had little effect on size reduction as it tended to produce a foam in the aqueous suspension being homogenised, cushioning the particles from the de-aggregatory effect of the cavitation generated by the ultrasonic process. Higher concentration of solids during homogenisation improved size reduction, but were not examined further as they tended to block the nozzle of the spray-dryer used to recover size reduced MCC as powder. Under the selected conditions of no SLS, 5 homogenisation cycles and 5% solids concentration, the median particle size of the treated MCC in aqueous suspension prior to spray-drying was estimated to be 16.4 ± 0.5 μm (95% confidence interval).

In a separate series of experiments the influence of increasing number of passes through the homogeniser was examined for both 5 and 10% MCC (Avicel® PH-101) suspensions, confirming that negligible further size reduction occurred by using greater than 5 cycles (Fig. 2). However, the

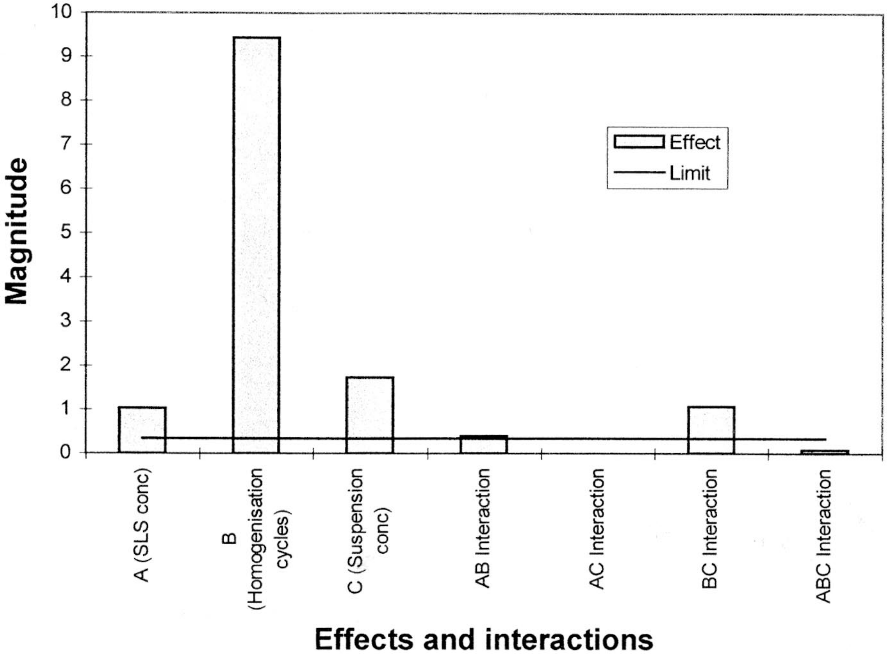

Fig. 1. Illustration of the magnitude of the factors examined and the interactions between them on the size reduction of MCC by ultrasonic homogenisation. The tie-line shows the magnitude above which the calculated effects and interactions are real, where all effects are illustrated as being positive for ease of presentation.

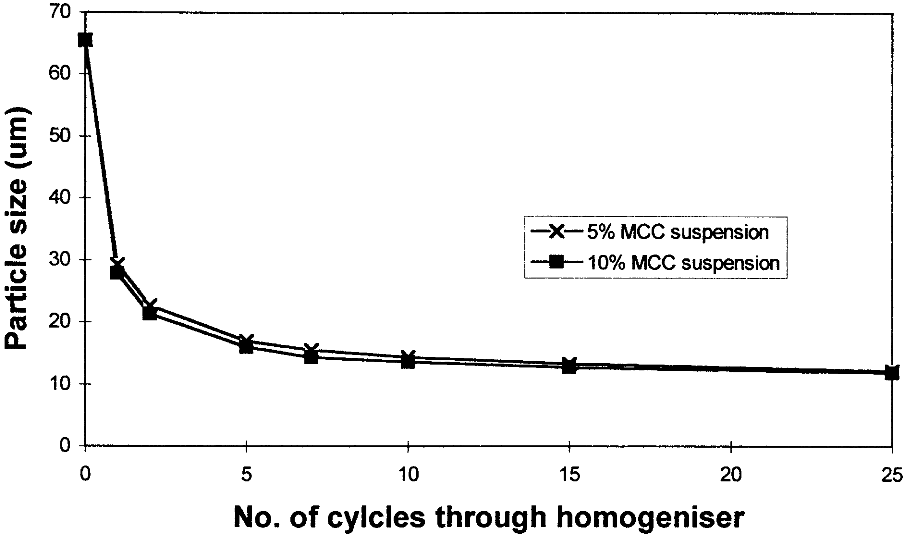

Fig. 2. Effect of homogenisation cycle number on the magnitude of size reduction of 5 and 10% MCC aqueous suspensions.

Table 3
Results of porosimetric study and median particle size of various grades of MCC

	Grade X	Grade Y	Grade C
Mercury total intrusion volume (ml/g)	2.25	2.03	1.62
Median pore diameter volume (μm)	3.23	3.21	16.56
Bulk density (g/ml)	0.33	0.37	0.46
Porosity (%)	73.5	74.3	74.9
Median particle size (μm)	12.6	10.6	56.4

polydispersity of size reduced samples continued to decline, reaching a minimum after 10 cycles.

3.4. Influence of de-aggregating agents on recovery and redispersal of size reduced MCC by spray-drying

Apart from the use of SLS, it was decided to investigate the effect of two other commonly used de-aggregating agents, sodium hexametaphosphate (SH) and sodium citrate (SC), on the recovery of MCC in size reduced form following spray-drying and on subsequent ease of re-dispersal of the dried product in water. Each agent was examined at two concentration levels 0.3125 and 0.625% using 5% MCC solids content and five homogenisation cycles. The D_{50} values for the various suspensions following size reduction ranged from 14.2 to 15.0 μm, confirming that none of the agents had a major effect on the ultimate particle size reduction achieved in the wet state from the control (Avicel® PH-101).

The various dry products recovered by spray-drying were re-constituted in a quantity of water equivalent to that lost by spray-drying and examined for particle size in the re-wetted state. The D_{50} values obtained ranged from 10.4 to 11.3 μm, confirming no major difference between the various de-aggregating agents examined and possible further size reduction occurred during the spray-drying to form products easily redispersed by gentle stirring in water as ultra-fine grade material. However, preferential collection of the finer particles as product in the cyclone separator may have contributed to the apparent size reduction observed on spray-drying.

3.5. Mercury porosimetry of size reduced grades of Avicel® PH-101

Mercury porosimetry was used to study the relationship between particle size and porous structure for two size reduced MCCs prepared by homogenisation prior to recovery by spray-drying without SLS (Grade X) or with SLS (1% added to homogenised suspension, Grade Y), compared to control (Avicel® PH-101, Grade C). The quantitative results of the porosimetry study, together with median particle size, are shown in Table 3. The equipment used was incapable of generating adequate pressure to effectively examine intra-particulate porosity, which was reported by Marshall and Sixsmith (1974) to have very fine diameters of ~0.003 μm for MCC.

The intrusion volumes for grades X and Y are very similar, and the lower value for grade C can be attributed to its broader size distribution as confirmed by particle sizing, whereby finer particles fill the inter-particulate space between larger particles. This improved packing of grade C is reflected in its higher bulk density, compared to the other two grades. The median pore diameter of both size reduced grades is lower, as the diameter of pores between fine particles tend to be smaller than for coarser powders (Hausner, 1967).

The shape of the cumulative intrusion versus pore diameter curves are typically sigmoidal for the three grades, as shown in Fig. 3. The control Avicel® PH-101 powder shows a sharp increase in cumulative intrusion volume when the pressure applied is adequate to cause filling of the inter-particulate pores with diameters ranging from ~8 to 30 μm, whereas the sharp increase is observed at lower pore diameters (~1–6 μm) for the size reduced grades. The total pore volume for grade Y is slightly lower than for grade X, as the SLS in grade Y coats the particles during the spray-drying process, as confirmed by SEM studies, to reduce inter-particulate porosity. Fig. 4 shows SEMs of Avicel® PH-101 before and after treatment with SLS, clearly showing that the surfactant coats the loosely bound arrangement of crystallites in the MCC aggregates.

3.6. Surface area of size reduced grades of Avicel® PH-101

The results of specific surface area determinations obtained for the various grades of MCC are shown in Table 4, using N_2 adsorption and Hg penetration methods with different sample pretreatments. The value of 1.42 m^2/g obtained for Avicel® PH-101 by mercury porosimetry is in good agreement with the value reported by Nakai et al. (1977) (1.5 m^2/g) using a similar procedure and values reported by Zografi et al. (1983) (~ 1.31–1.44 m^2/g) using both nitrogen and krypton adsorption techniques. In this project the observed lower value of 0.98 m^2/g for Avicel® PH-101, determined by the nitrogen adsorption technique, may have resulted from rapid moisture pick-up from the atmosphere by prepared samples prior to being run, despite attempts to minimise this effect. This residual moisture present within samples would freeze at liquid nitrogen temperatures used during the N_2 adsorption studies, blocking access to the porous MCC surfaces, unlike the mercury intrusion studies, which were carried out at room temperature (~ 20°C). These observations suggest that the mercury intrusion technique may give results more representative of the true value.

Both techniques indicate that the specific surface area of size reduced grades is significantly larger than the coarser control MCC, in keeping with larger surface area per equivalent weight expected with finer particles. The slightly bigger specific surface area reported for the SLS treated ultra-fine MCC, compared to in its absence, probably reflects its observed finer particle size and the increased surface area due to precipitation of the surfactant on the surface of the MCC particles.

3.7. DSC and X-ray diffraction analysis of size reduced grades of Avicel® PH-101

The water associated with MCC may be classified into (a) tightly bound water ('non-freezable') associated chemically and physically with mainly amorphous regions, where mobility occurs at temperatures above −103°C approx, (b) loosely bound water ('freezable', mobility above 0°C) and (c) unbound water with properties similar to normal bulk water. Consequently low temperature DSC studies that can distinguish between 'non-freezable' and 'freezable' water present in samples, can be used to provide an estimate of the amount of amorphous regions in MCC. Samples of grades C, X and Y were hydrated to variable levels and endotherm curves for samples of X are

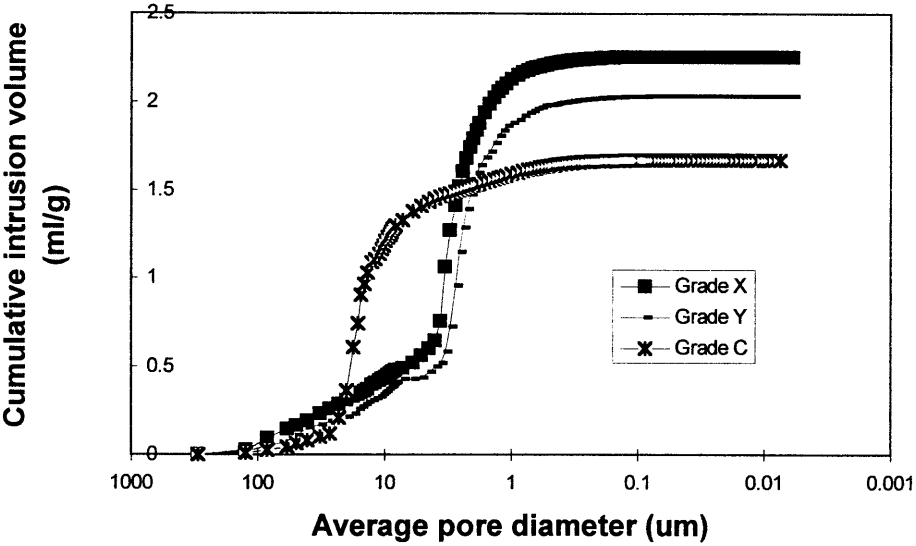

Fig. 3. Cumulative mercury intrusion curves for grades C, X and Y MCC.

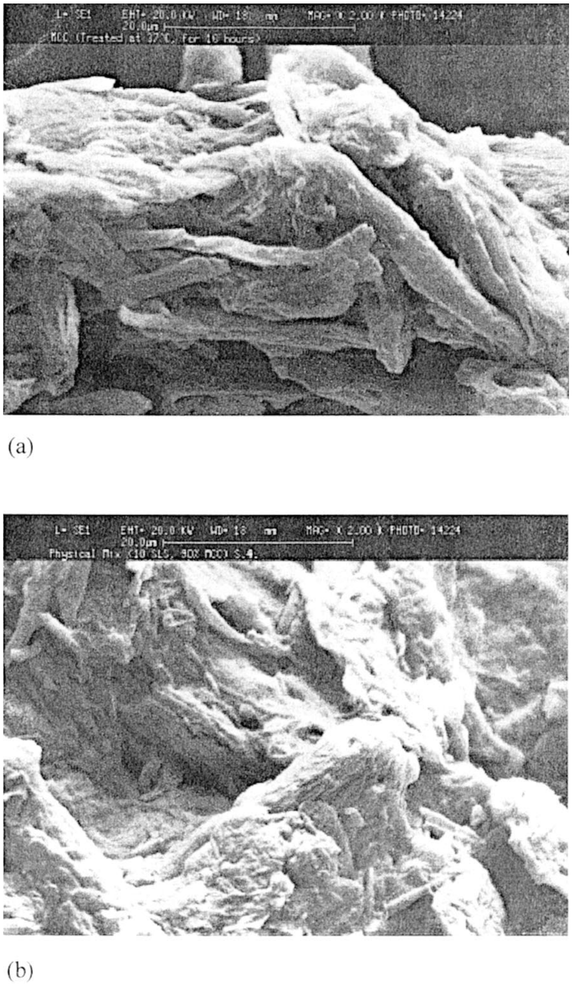

Fig. 4. SEM of Avicel® PH-101 before (a) and after (b) treatment with SLS solution.

shown in Fig. 5, indicating absence of a peak at low hydration levels indicative of a phase transition with 0°C onset temperature. Similar type plots were constructed for the other two grades.

Plots of ΔH per g polymer as a function of water content (% w/w) were prepared as shown in Fig. 6 for samples of grade X, the slopes of which were used to estimate the enthalpy (ΔH_{endo}) associated with the event and the inflections to estimate the 'non-freezable' water content, the results of which for the three grades are shown in Table 5.

The calculated enthalpy for Avicel® PH-101 is 79.66 cal/g using the endothermic data. When this powder is size reduced by homogenisation to produce grade X, the calculated enthalpy for the new grade falls to 73.3 cal/g. This suggests that the water phase is more dispersed in grade X relative to grade C. This is due to the smaller particle size in the new grade, which creates a more tortuous matrix or pathway into and around which the water must spread, thus increasing the magnitude of the mixing enthalpy. In contrast, the calculated enthalpy for grade Y (82.54 cal/g) is larger than the control grade C and is very close to that calculated for bulk pure water (83.38 cal/g). Thus the SLS in grade Y appears to reduce the magnitude of the mixing enthalpy (energy) associated with dispersing the water phase around the MCC particles, due to its ability to promote wetting. As the calculated 'non-freezable' water content is predominantly tightly bound to the amorphous regions of the MCC, consequently grade X with minimum % bound appears from these thermal studies to be the most crystalline and Avicel® PH-101 the least crystalline of the three grades examined.

Table 4
Specific surface area of various MCC grades measured by mercury porosimetry (Hg) or nitrogen adsorption (N_2) methods

Method	Grade	Pre-treatment	Surface area (m^2/g)
Hg	C	Heated at 70°C for 24 h followed by vacuuming at 50 µm Hg	1.42
	X		3.52
	Y		3.73
N_2	C	Heated at 70°C for 24 h under vacuum followed by helium purge for 3 h at 70°C	0.98
	X		2.44
	Y		2.95

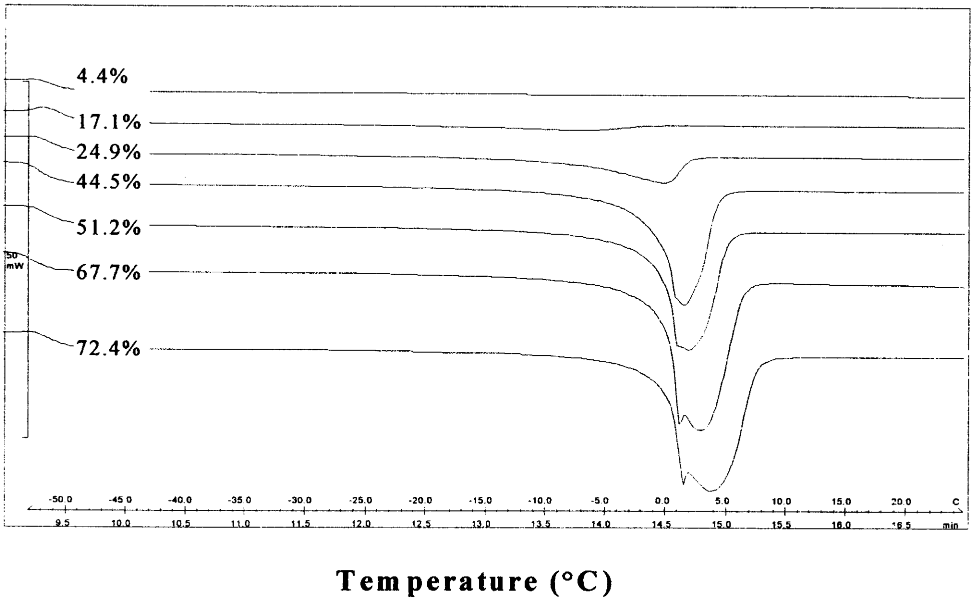

Fig. 5. DSC endotherms for hydrated grade X as a function of water content (scan rate 10 K/min).

X-ray diffraction studies were performed on the three powdered grades to confirm the results of crystallinity inferred from the DSC studies. The averaged x-ray diffractograms for the three MCC powder grades are shown in Fig. 7, indicating highly native crystalline cellulose of type I form, as characterised by peaks at 14, 16 and 22.6° 2θ. Type II cellulose, formed by vigorous manufacturing techniques, has characteristic peaks at 12 and 20° 2θ (Landin et al., 1993). Thus the original manufacturing process for grade C and the subsequent homogenisation/spray-drying for grades X and Y are mild enough to maintain the cellulose in its native form.

The cystallinity index was calculated using intensity measurements at 22.6° and 19.0° (amorphous background) 2θ, as used by Chatrath et al. (1991), and gave values of 84.49, 83.93 and 84.4% for grades C, X and Y respectively. Whereas quantitatively the percentage crystallinity determined by both methods are not greatly dissimilar, the ranking of the grades by each technique is inverse. In keeping with the observation of Nelson and O'Connor (1964) on ball-milling cellulose samples, cavitation forces generated during the homogenisation of grades X and Y should cause break-up of some of the crystalline regions in Avicel® PH-101, rendering the product more amorphous, with some protection being afforded by foam production from added SLS in the Y grade, explaining the results of crystallinity studies by the X-ray diffraction technique. The anomalous results obtained with the DSC technique are probably related to the reduction in MCC particle size, creating a more tortuous matrix around which water must diffuse. This could hinder the distribution of water to all of the amorphous regions of the MCC, particularly in

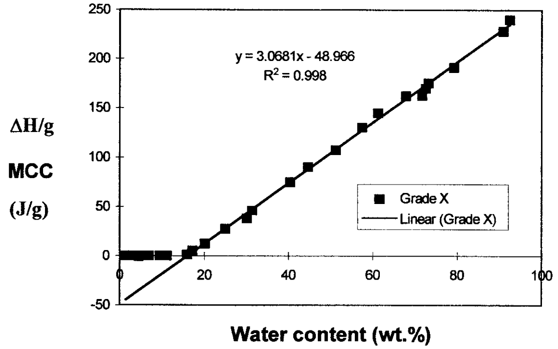

Fig. 6. Enthalpies per g of grade X MCC versus water content.

Table 5
Calculated 'non-freezable' water contents, enthalpies (ΔH_{endo}), regression fits to 'freezable' water data and estimated % crystallinity from the endothermic DSC results

Grade	'Non-freezable' (%)	ΔH_{endo} (cal/g)	Regression fit to 'freezable' water data	Estimated % crystallinity
C	18.81	79.66	$W_f = 0.98W - 17.5$	81.19
X	15.96	73.30	$W_f = 0.98W - 15.0$	84.04
Y	18.38	82.54	$W_f = 1.0W - 18.4$	81.62

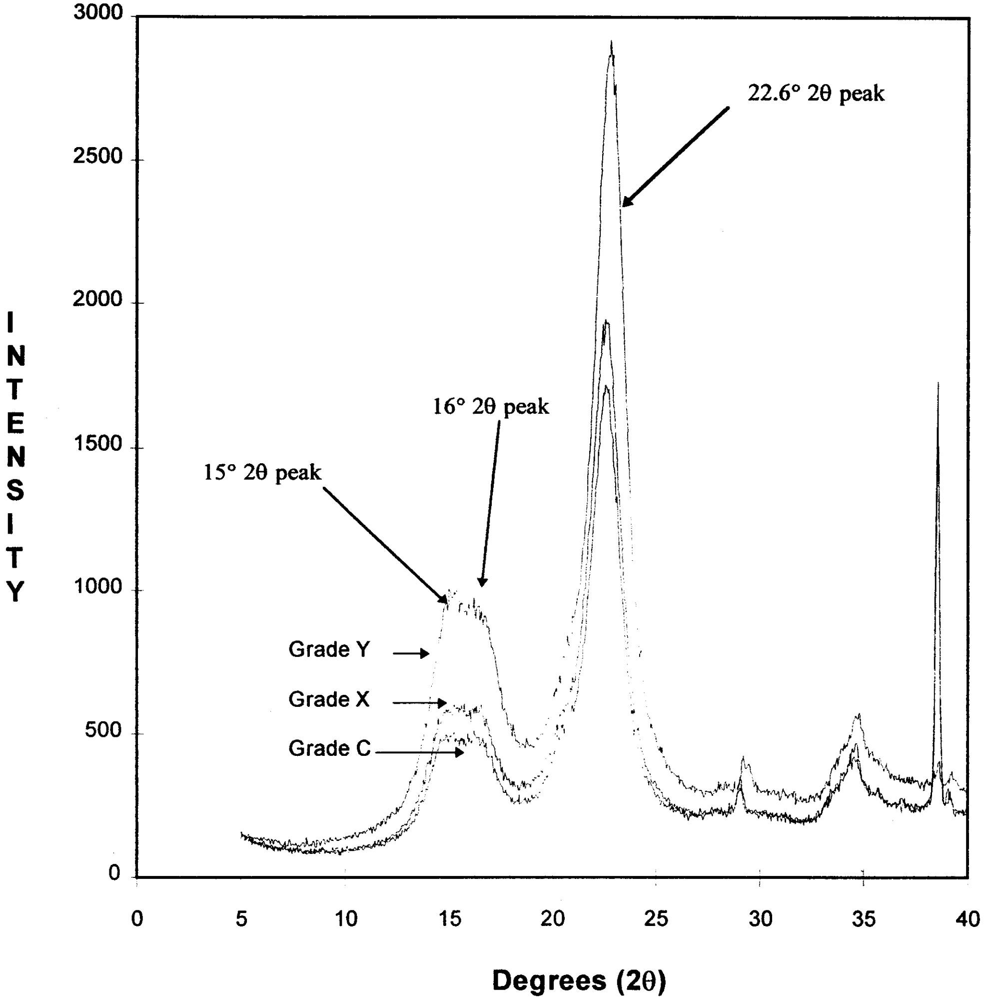

Fig. 7. X-ray diffraction patterns of MCC grades.

grade X, resulting in underestimation of the actual amount of tightly bound water and accordingly greater inferred crystallinity. Pouchly et al. (1979) likewise cautioned about the interpretation of DSC data for cellulose, as heavily hydrated samples may behave in a similar fashion to those with low water content since non-equilibrium kinetic factors such as reduced water diffusivity, stearic constraints due to the rigid polymer matrix, frozen bulk-like water and water coagulation collectively influence the thermal response.

Similar analysis was applied to the exothermic data obtained by DSC, with no thermal events being observed below 18–20% water content, indicating that such water is tightly bound in the three grades of MCC examined. The calculated 'non-freezable' water contents for grades C, X and Y are 17.74, 15.37 and 17.14% respectively, all being lower than the corresponding values calculated from the endothermic data. This agrees with previously reported studies (Quinn et al., 1988), where super-cooling terminates in rapid nucleation, inducing a greater change in heat capacity to which a DSC is sensitive (Coyle et al., 1996).

According to Blair et al. (1990), a 1:1 binding stoichiometric ratio exists (i.e. one molecule of water binds to one anhydroglucose binding site) when the level of tightly bound water approximates 19%. This binding stoichiometry would appear to have been achieved for the three grades of MCC examined in this study, facilitated by hydrating samples for sufficiently long period (>1 week) prior to DSC analysis. This agrees with the proposed three stage binding model involving (i) water binding tightly to the anhydroglucose units and linking adjacent units (i.e. 2 hydrogen bonds per water molecule corresponding to $\sim 10\%$), (ii) breaking of some of the initial bonds formed between water and cellulose, with addition of extra water molecules to bind at the vacated anhydoglucose sites ($\sim 19\%$), and (iii) rapid onset with further water content of hydrogen bonds between water molecules (i.e. within loosely bound and 'bulk-like' water).

4. Conclusions

Two new ultra-fine grades of MCC (median size ~ 15 μm), one containing particles coated with SLS, have been produced by conveniently applying an ultrasonic homogenisation step prior to recovery as dry powders by spray-drying, which readily redisperse in water. The type of homogeniser and its conditions of use could be modified to produce even finer grades of MCC. Commercial production of such grades should result in the finest grades yet available, apart from the so-called 'colloidal' ranges. The new grades have been extensively characterised, highlighting important differences in particle size range, appearance, porosity, surface area, ease of wetting and crystallinity, compared to coarser Avicel® PH-101.

A subsequent paper will examine the unique functionality of these new grades in a range of model dosage forms, with suitable correlation to their characterisation as described in this report.

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