Colloid Polym Sci 278:597–607 (2000)

ORIGINAL CONTRIBUTION

M. Jumaa
F. El Saleh
I. Hassan
B. W. Müller
P. Kleinebudde

Influence of cellulose type on the properties of extruded pellets. Part I. Physicochemical characterisation of the cellulose types after homogenisation

Received: 27 July 1999
Accepted: 15 December 1999

M. Jumaa · F. El Saleh · B. W. Müller
Department of Pharmaceutics & Biopharmaceutics,
Christian Albrecht University Kiel
Kiel, Germany

I. Hassan
Department of Pharmaceutics & Biopharmaceutics, Damascus University
Damascus, Syria

P. Kleinebudde (✉)
Institute of Pharmaceutics & Biopharmaceutics
Martin Luther University,
Halle-Wittenberg
Wolfgang-Langenbeck-Strasse 4
06120 Halle, Germany
e-mail:
kleinebudde@pharmazie.uni-halle.de
Tel.: +49-345-5525167
Fax: +49-345-5527029

Abstract The physicochemical properties of different types of powdered cellulose (PC) and microcrystalline cellulose (MCC) were studied by examining the changes in particle size, viscosity and specific surface area after a homogenisation process. An additional characterisation was carried out using X-ray diffractometry. A preliminary investigation using a type of MCC showed that increasing the homogenisation pressure and the number of passage cycles led to a significant decrease in the particle size and simultaneously to a remarkable increase in the specific surface area and viscosity. Most MCC types showed the same pattern during the homogenisation process. "Colloidal" MCC displayed a higher viscosity than the others but without significant change in the viscosity after different homogenisation cycles. In contrast to this behaviour of the MCCs, the PCs showed no remarkable change in the particle size but did show a marked change in their viscosity. Furthermore, only MCC suspensions, with the exception of "colloidal" MCC, agglomerated after the homogenisation process, whereas this was not seen in the PC suspensions. Hence, since the MCC types as well as the PC types originally had the same chemical structure, this different behaviour among these types can only be attributed to their different physical properties.

Key words Powdered cellulose · Microcrystalline cellulose · Physicochemical properties · Homogenisation process

Introduction

Due to its several advantages, microcrystalline cellulose (MCC) is widely used as an excipient in pharmaceutical manufacturing. One of its most important uses is in the production of pellets for both controlled release and conventional dosage forms [1–3]. Cellulose, obtained as a pulp from fibrous plant materials, consists of amorphous cellulose areas and, additionally, well-ordered crystalline regions. MCC is prepared by treating wood pulp or linters with dilute mineral acid and is described as a purified, partially depolymerised cellulose [4, 5] with a degree of polymerisation (DP) below 350. MCC is basically made of crystallites of colloidal size. The crystallites aggregate, forming particles of about 15–20-μm diameter. These aggregates in turn agglomerate during drying of the cellulose slurry, so a final mean particle size between 20 and 200 μm is reached. Powdered cellulose (PC) is obtained from wood pulp by mechanical treatment and possesses a DP above 440.

In spite of the widespread use of MCCs and/or PCs, there is little work dealing with the relation of the physicochemical properties of these materials, especially concerning the particle size and rheological behaviour, and their suitability in pharmaceutical processing. For example, the physical properties of MCCs (Avicel PH 101, PH 102 and Dancyl) were studied in different ways to establish if there were reasons for describing the MCCs to be agglomerates of smaller individual particles [6, 7]. It was found that using PCs and/or MCCs could

greatly affect the physical properties of the resulting product [8]. Furthermore, two models recently appeared in the literature dealing with the behaviour of MCCs during the pelletisation process: the models aimed to describe the changes in the physical properties of MCCs during this process [9, 10].

The overall objective of this study is to investigate how mechanical processing (homogenisation) influences the physicochemical properties and rheological behaviour of MCC and PC with the aim to understand better the properties of these important excipients. A further aim is to find out if there is any relevance between these properties and the resulting product, especially concerning the pelletisation process (in the second part of this work).

Experimental

Materials

Avicel PH 101, PH 102, PH 200 and PH 301 and RC 591 were supplied by FMC (Philadelphia, USA). Prosolv SMCC 50 was purchased from Mendell (Patterson, USA). Avicel PH is pure MCC, while Avicel RC is MCC coprocessed with approximately 11% sodium carboxymethylcellulose as a protecting colloid. Prosolv is MCC coprocessed with 0.5% colloidal silicon dioxide. Two types of PC, Elcema P050 and Elcema P100, were furnished by Degussa (Frankfurt am Main, Germany). Doubled-distilled water was used for all preparations.

The properties, mean particle size, degree of crystallinity (CI) and DP, of the different types according to the manufacturer and our measurements are listed in Table 1.

Methods

Preparation of the suspensions and the homogenisation process

The corresponding amount of MCC or PC was dispersed in 100-ml double-distilled water using a magnetic stirrer. Some of this premixture (40 ml) was presuspended using an Ultra-Turrax T25 (Jahnke & Kunkel, Staufen, Germany) at 8000 rpm for 3 min in order to obtain a homogeneous presuspension. After this, the presuspension was passed through a high-pressure homogeniser (Micron Lab 40, APV Gaulin, Lübeck, Germany). Warm water was circulated around the homogenisation unit to maintain the temperature at 40 °C in order to avoid any influence of the temperature, which can rise to 37 °C during the homogenisation [11]. Different formulations were produced by variation of the homogenisation pressure and the number of cycles as well as the concentration of the MCC (in the case of the preliminary investigation using Avicel PH 101). Each formulation was prepared twice.

Suspension evaluation

The particle size distribution of the suspensions was obtained using a laser diffraction analyser (LDA) (Helos, Sympatec, Clausthal-Zellerfeld, Germany) at a focal length of 50 mm, corresponding to a measurement range of 0.45–100 μm. For this investigation, a sufficient amount of suspension (to achieve a suitable intensity) was dispersed in a stirred sample filled with deionised water. Three measurements were made on each suspension before and after ultrasonication for 90 s (60 W, 40 kHz). The sonication of the MCC suspension will break down the agglomerates obtained during the homogenisation process. A short sonication time was chosen, since the cellulose fibers are known to be broken by ultrasonic treatment [5]; however, the time chosen is very short in comparison to the times reported elsewhere [5, 7] and will only affect the MCC agglomerates [12].

The agglomeration index can also be used in order to investigate the agglomeration behaviour [13]. The agglomeration index is the ratio of mean diameter (D_{50}) before and after sonication. A nonagglomerated suspension displays an agglomeration index of 1.

The resultant particle size distributions were averaged. The suspensions were characterised by their D_{50} and D_{99} quantiles of the volumetric distribution (that means 50 or 99% were below the given size). Additionally, the specific surface area, S_v, which is based on spherical particles, was also calculated (obtained directly from LDA), because generally the reduction in the size of the particles in the dispersed phase is accompanied by an increase in the specific surface area [14]. Thus, the determination of this value can be of assistance in studying the influence of the homogenisation process on the particle size. Furthermore, in order to investigate whether the suspensions contain colloidal particles (fine particles), the suspensions were measured using photon correlation spectroscopy (PCS) covering the size range from 5 nm to approximately 3 μm (Malvern spectrometer RR 102, Malvern, UK, with a He-Ne laser, $\lambda = 632.8$ nm, Siemens, Germany). PCS measurements were carried out because PCS can give more information about the presence of colloidal particles than LDA [15]. For size analysis approximately 1 μl suspension was added to 1 ml distilled water in order to obtain the optimum scattering intensity. As for the LDA measurements, the PCS measurements were carried out before and after ultrasonic treatment (90 s). The nonhomogenised suspensions

Table 1 Properties of the various cellulose types investigated

Cellulose type	Mean particle size (μm)		Degree of crystallinity (%)		Degree of polymerisation
	Manufacturer	Our measurements	Refs. [9, 21]	Our measurements	Manufacturer
PH 101	50.0	51.5	65.3	68.6	230
Prosolv	50.0	57.8	–	71.8	230
PH 102	90.0	129.8	76.0	74.6	230
PH 105	20.0	19.9	68.0	68.1	230
PH 200	200.0	144.3	63.3	67.5	230
PH 301	50.0	52.9	74.3	76.4	155
RC 591	–	34.8	–	70.1	–
Elcema P050	–	30.7	–	35.8	–
Elcema P100	–	50.5	–	44.3	–

were characterised in the same way as the homogenised one (after stirring in order to get a homogeneous suspension). The wet extrudates were first soaked in water and then gently stirred in order to obtain a suspension. After that, the extrudates were characterised as for the homogenised samples.

Determination of the viscosity

Further characterisation of the cellulose suspensions was obtained through measurements of slurry viscosity. The viscosity was measured using a Rheoanalyzer rotation viscometer (Contraves, Gieres, France) equipped with coaxial cylinders. A sufficient, constant amount of the suspension was filled into the measurement unit (MS-DIN 114). During the sample measurement the rate of shear was increased to 488 s^{-1} and the viscosity was calculated from the recorded shear stress. Two samples of the same suspension were investigated and each sample was measured twice. The results were averaged.

X-ray diffraction assay

The CI was calculated from X-ray diffractograms according to Knolle and Jayme [16]. Powder X-ray diffraction patterns of the various cellulose types were determined using an X-ray diffractometer (Stoe Cie, Darmstadt, Germany) with a rotating anode. The transmission technique was carried out with Cu k_α radiation monochromatised at a wavelength of 1.5405 Å. All measurements were carried out at a voltage of 40 kV and a current of 200 mA. The samples were scanned over the region 5–50° 2θ at a rate of 1° 2θ each 10 s and the signals were detected using a position-sensitive detector.

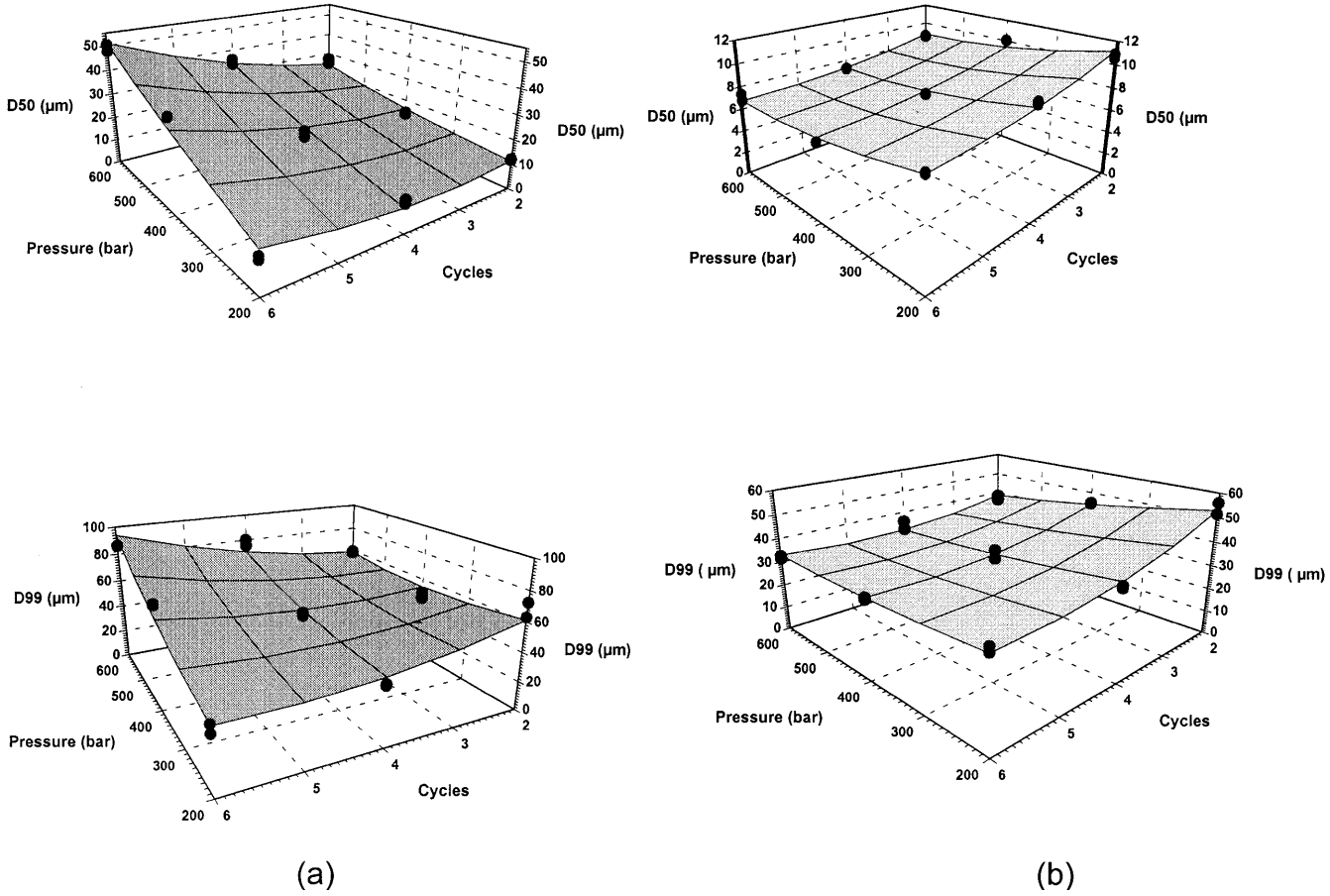
Results

Effect of the homogenisation process on the particle size of MCC suspensions

Avicel PH 101 suspension

The particle size and particle size distribution of PH 101 were greatly affected by changing the homogenisation conditions (pressure and cycles). Increasing the homogenisation pressure and the number of homogenisation cycles leads to a remarkable decrease in the size of the suspension particles (Figs. 1b, 2b). It is also clear that the mean particle sizes (D_{50}) as well as the number of large particles (D_{99}) were reduced by increasing the shear and the time of the homogenisation (Fig. 2b); however, varying the concentration of Avicel PH 101 (3, 6 and 9%) did not change this pattern and the same behaviour was observed. Therefore, only the

Fig. 1 Influence of the homogenisation conditions on the particle size of Avicel PH 101 (3%) **a** before and **b** after sonication



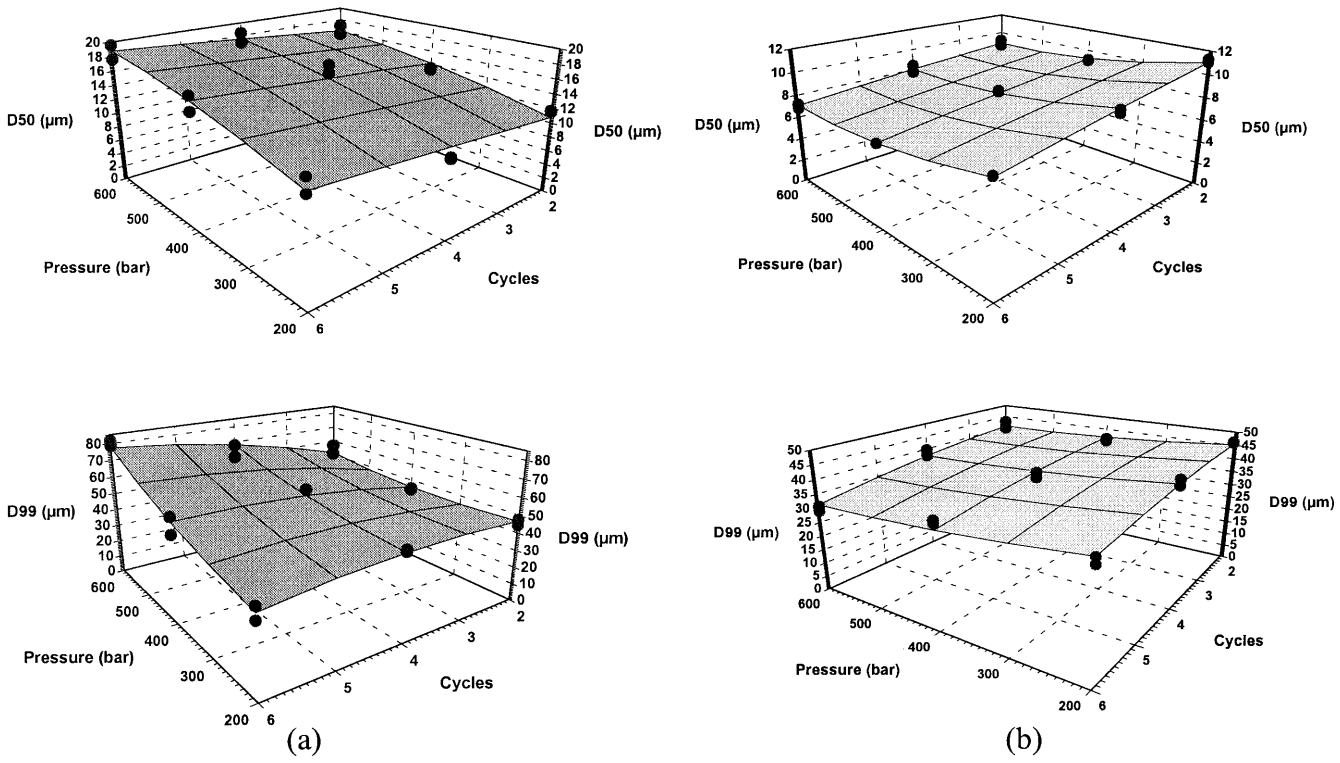


Fig. 2 Influence of the homogenisation conditions on the particle size of Avicel PH 101 (9%) **a** before and **b** after sonication

3 and 9% results are shown. It is worthwhile noting, however, that increases in the number of homogenisation cycles and the pressure were accompanied monotonically by a marked agglomeration of MCC particles (Figs. 1a, 2a). The number of these agglomerates could be decreased significantly by sonication of the suspension.

Moreover, this can also be seen from the S_V results as well as from the agglomeration index. Using the suspension with 9% as an example, S_V values showed a marked decrease as the homogenisation pressure as well as the number of homogenisation cycles were increased (Fig. 3a), indicating the formation of large agglomerated particles. In contrast to this, after sonication the S_V values showed a significant increase as the pressure and the number of cycles were increased, indicating a breakdown of the agglomerates obtained by homogenisation to the individual particles (Fig. 3b). In addition, the agglomeration index also supports these observations, with the index increasing on increasing the strength of the homogenisation conditions. Using the D_{50} values of the 9% suspension at 600 bar once again as an example, pouring the suspension two, four and six times through the high-pressure homogeniser led to an agglomeration index of 1.83, 2.18 and 2.8, respectively. This indicates clearly the agglomeration of MCC particles during the homogenisation process. This agglomeration increases under stronger homogenisation conditions.

Suspensions of different PC and MCC types

Further trials were carried out using PCs as well as MCCs. The particle sizes of the resultant homogenised suspensions was compared with the particle size of PH 101. In these trials the concentration of 9% (w/w) and the homogenisation pressure (400 bar) were kept constant. The exception was RC 591, where a suspension with a concentration of 3% was investigated. A further increase in the concentration of RC 591 was not possible because the suspension became too viscous and it could not be poured through the homogeniser.

The particle size of the suspensions was estimated after two, four and six cycles corresponding to the preliminary investigation with Avicel PH 101. As shown in Fig. 4b, most MCC types behave similarly and no noticeable distinction between them could be observed. Passing the suspension more times through the homogeniser led to the formation of large agglomerated particles (Fig. 4a), which disaggregated to individual particles after the application of sonication (the exception was, however, RC 591). In contrast to the MCCs, the PCs (Elcema P050 and P100) behaved differently. No remarkable reduction in their particle size was observed either before sonication or after it and

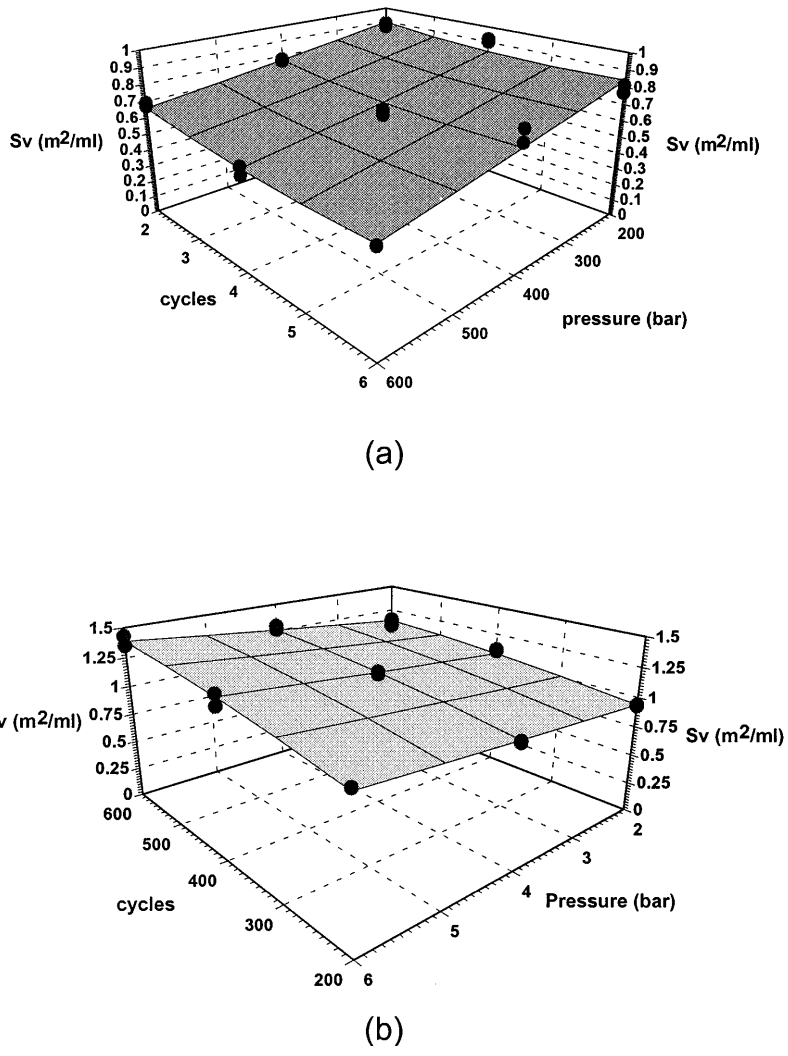


Fig. 3 Influence of the homogenisation conditions on the S_v values of Avicel PH 101 (9%) **a** before and **b** after sonication

increasing the number of pouring times also had no effect (Figs. 4a, b). Hence, the MCCs display different behaviour in comparison to the PCs according to these results.

The S_v values of the other MCC types showed clearly that they behaved like PH 101, displaying the same pattern (the exception was again RC 591 as shown in Fig. 5b), whereas the PCs once more showed contrasting behaviour. MCCs showed a decrease in their S_V values after the homogenisation (Fig. 5a); however, a marked increase in the S_V values after sonication was observed (Fig. 5a), indicating the presence of large agglomerated particles. Conversely, the homogenisation of the PC suspensions resulted in a negligible change in the S_V values, which were also unaffected after the ultrasonic treatment (Fig. 5b). In addition to S_V, calculating the agglomeration index after six cycles for all the cellulose types also showed the same picture. The agglomeration indices obtained for PH 301, PH 200, PH 102, Prosolv 50, RC 591, Elcema P 050 and Elcema P100 were 1.65, 1.69, 1.95, 2.46, 1.02, 1.04 and 1.02, respectively. These agglomeration indices indicate clearly that the MCCs contained large agglomerated particles in contrast to the PCs and RC 591.

Thus, it could be seen from the LDA and S_V values that the homogenisation of the MCC suspensions led to the breakdown and agglomeration of the cellulose particles, where the shear force was not able to reduce the particle size of the PC suspensions. Similar behaviour was also observed when preparing suspensions for national formulary (a collection of monographs for pharmaceutical excipients), and this behaviour was used formerly as an identity test for MCC [17].

Moreover, according to the PCS measurements, only the MCC suspensions showed an acceptable correlation function, indicating the presence of particles in the colloidal range as an acceptable PI should be smaller than 0.35 otherwise the resulting correlation function would be not satisfactory. The PC suspensions displayed unsatisfactory correlation, indicating that the

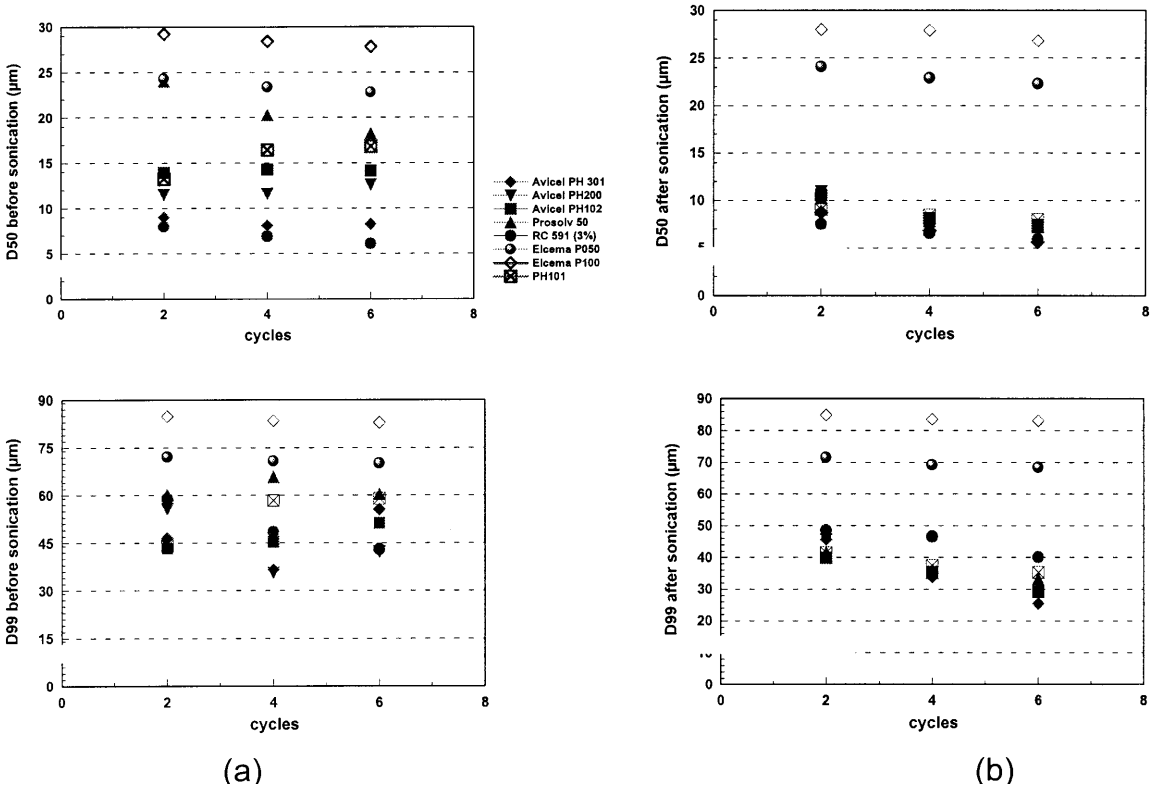


Fig. 4 Influence of the homogenisation cycles at 400 bar pressure on the particle size of different microcrystalline cellulose (*MCC*) and powdered cellulose (*PC*) types **a** before and **b** after sonication

suspensions did not contain such small particles (Table 2).

Effect of the extrusion process on the particle size of various cellulose types

In a previous article, it was suggested that in order to explain the process of the production of pellets by extrusion/spheronisation the MCCs have to be broken down into smaller particles by shear forces acting during the extrusion process [9]. To support this proposition wet extrudates were taken directly from the extruder and then soaked in water. The particle sizes of the various extrudate suspensions as well as those of various powder suspensions were characterised using PCS and LDA before and after sonication. The results are summarised in Table 3. From these results it is obvious that the size of all the MCCs was greatly reduced after the extrusion process in comparison to the powder suspensions, whereas the PCs did not show a significant reduction in their particle size. The MCCs again displayed the affinity to agglomerate and these agglomerates were destroyed after sonication. Moreover, colloidal particles could only be detected using PCS measurements (after sonication) in MCC extrudate suspensions, whereas in the case of PC no correlation was marked. Thus, according to these results it can be deduced that the particle size of the extrudate suspensions corresponds well with the particle size after homogenisation.

Influence of the homogenisation process on the suspension viscosity

Increasing the concentration of PH 101 led to a monotonic increase in suspension viscosity; therefore only the influence of the homogenisation pressure and the number of homogenisation cycles on the suspension viscosity at a constant concentration are presented. As shown in Fig. 6. the homogenisation process produced viscous suspensions, and increases in the homogenisation pressure and the number of cycles were accompanied by a concomitant increase in suspension viscosity. Furthermore, over a fairly wide range of shear rate thinning behaviour was observed for the PH 101 suspension (data not shown). Beyond the yield value, increasing rates of shear led to a decreasing apparent viscosity. The suspension liquefies reversibly upon shaking and solidifies upon standing, the process being time-dependent. These findings were noted for all lots of MCC studied, demonstrating that the homogenisation process led to an increased suspension viscosity of the material being tested (Fig. 6) (the exception was

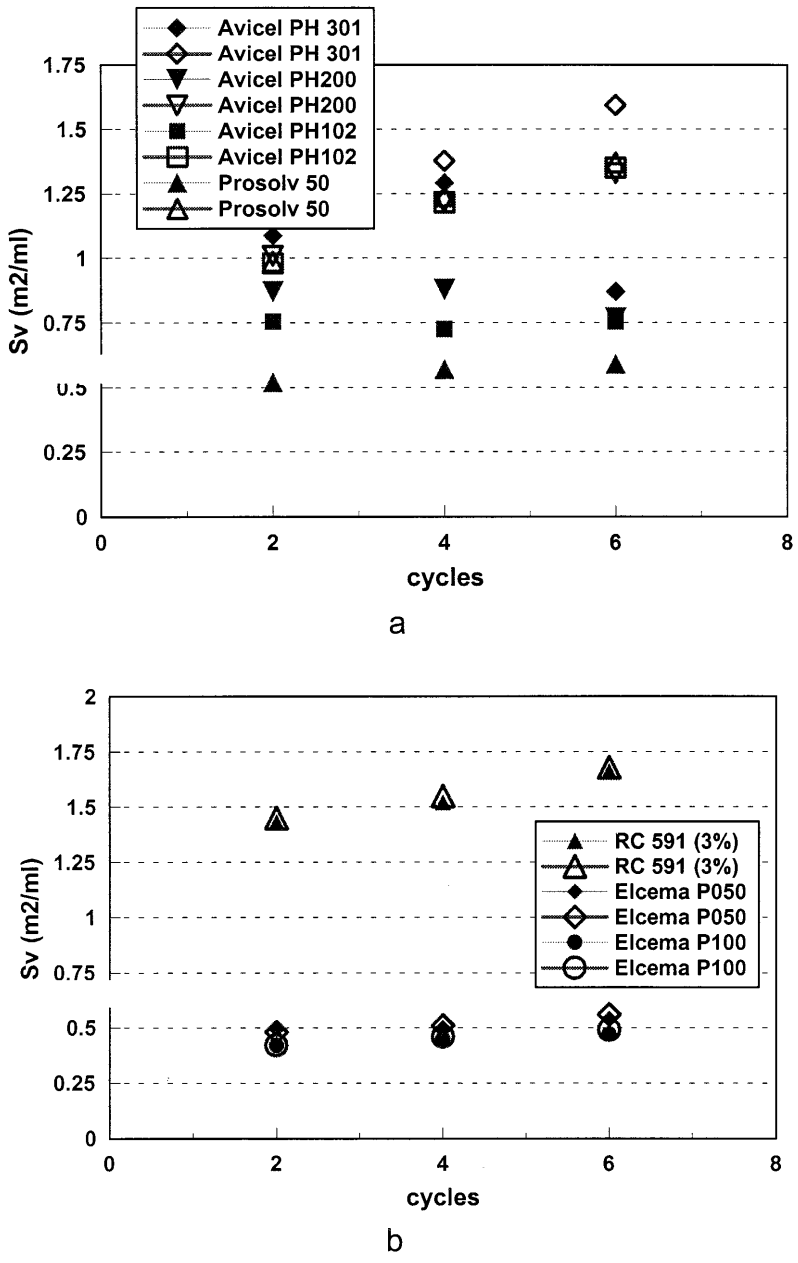


Fig. 5 Influence of the homogenisation cycles at 400 bar pressure on the S_v values of different MCC and PC types (9%) before (*filled symbols*) and after (*open symbols*) sonication

Table 2 Photon correlation spectroscopy (*PCS*) values of different cellulose types with 9% concentration (w/w) after six cycles at a pressure of 600 bar

Cellulose type	Mean particle size obtained from PCS (nm)
Avicel PH 101	735 ± 75
Avicel PH 102	755 ± 130
Avicel PH 200	834 ± 125
Avicel PH 301	449 ± 93
Prosolv 50	817 ± 87
RC 591	620 ± 49
Elcema P050	No correlation
Elcema P100	No correlation

again RC 591 as shown in Fig. 7b). From Fig. 7a it can also be noted that the PH 301 suspension showed the highest viscosity among the other Avicel PH types. Moreover, as mentioned before the MCC RC 591 concentration was 3%, and a comparison between the viscosity of RC 591, PH 101 and PH 301 using 3% suspensions was carried out. Figure 7b shows that RC 591 has the highest viscosity, whereas PH 101 has the lowest one.

With regard to the PC rheological behaviour, a marked increase in the viscosity of the suspensions was also noted after the homogenisation process (Fig. 7a), but the viscosity was less dependent on the shear rate.

Table 3 Effect of extrusion process on the particle size of various cellulose types (*B* before sonication and *A* after sonication)

Cellulose type	Powder suspension				Extrudate suspension				PCs (nm) extrudate
	D_{50}		D_{99}		D_{50}		D_{99}		
	B	A	B	A	B	A	B	A	
PH 101	47.3	24.3	86.3	68.9	12.5	5.9	54.2	32.9	671.9
PH 102	57.2	24.2	86.6	72.6	21.7	10.8	85.1	38.6	965.8
PH 105	22.5	19.4	59.7	55.8	9.4	6.8	47.6	31.4	792.5
PH 200	45.8	23.9	86.4	73.6	9.9	6.9	52.1	33.6	873.7
PH 301	47.6	22.5	86.4	63.3	13.7	6.8	72.4	31.5	543.7
Elcema P050	27.3	26.5	80.3	78.2	22.7	22.3	71.8	71.2	No correlation detected

Crystallinity of the various cellulose types

The crystallinity results of the MCC types show that PH 301 and PH 102 displayed the highest values, whereas the others displayed lower and similar values (Table 1). Moreover, most types also exhibited a similar X-ray pattern (Fig. 8). An exception was Avicel RC 591, which has a similar value in comparison with PH 101 or PH 200 (Table 1) but a different X-ray pattern (Fig. 8). The (NaCMC) contained in RC 591 may be the reason for this difference. These results are in good agreement with the data of Rowe et al. [18], who showed that Avicel PH 101, PH 103, PH 105 and PH 200 displayed similar crystallinity. They surmised, therefore, that the differences seen in the processing of these materials cannot only be attributed to the crystallinity. In contrast to this, PCs displayed different behaviour, as they showed lower crystallinity in comparison to MCCs (Table 1) and different X-ray patterns (Fig. 8).

Discussion

From the results presented here it is evident that the PCs behaved differently during the homogenisation process in comparison with the MCCs. Clearly, the particle size of the MCC suspensions (with the exception of RC 591) decreased during the homogenisation process, and there was no difference between all MCC types (PH 301 has, however, the lowest particle size) although there were big differences in the mean particle size of the original powders (Table 1). The MCC suspensions agglomerated during the homogenisation and individual particles were obtained once more by disintegration of the agglomerates using ultrasonic treatment. The different behaviour of RC 591 could be attributed in most instances to its special structure, because it is the basic colloidal grade of MCC. This material is quite different in appearance from the PH types: it has a coating of NaCMC on the MCC crystallites. In the presence of water and under mild shear stress, RC 591 particles swell quickly and are then peptised to yield a dispersion of separate crystallite aggregates; therefore, this RC type showed a high

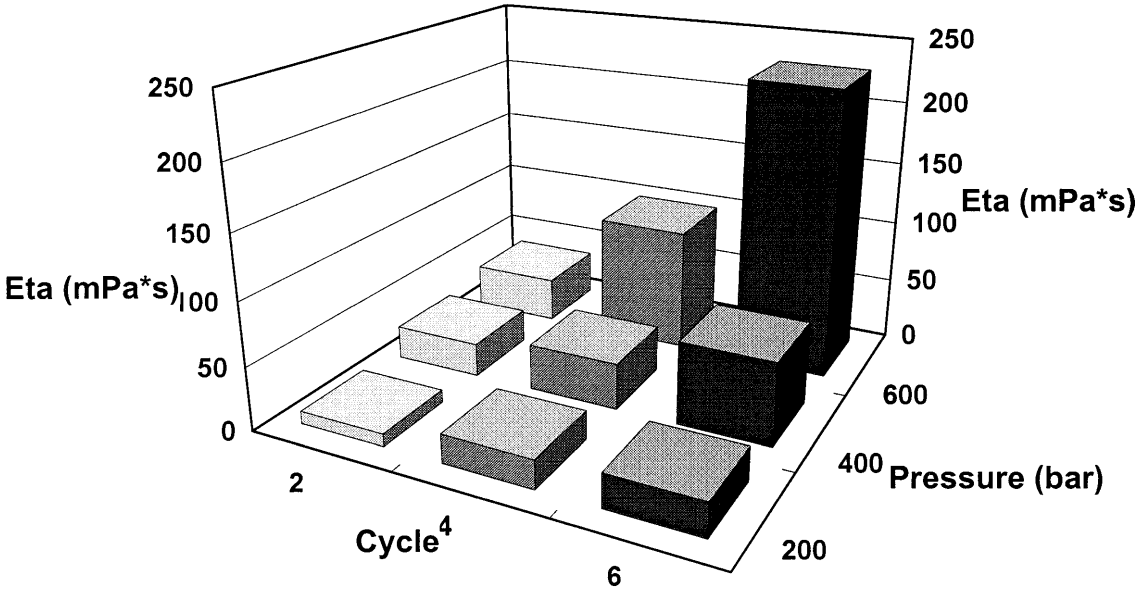


Fig. 6 Influence of the homogenisation conditions on the viscosity of the PH 101 suspension (9%) at a shear rate of 488 s^{-1}

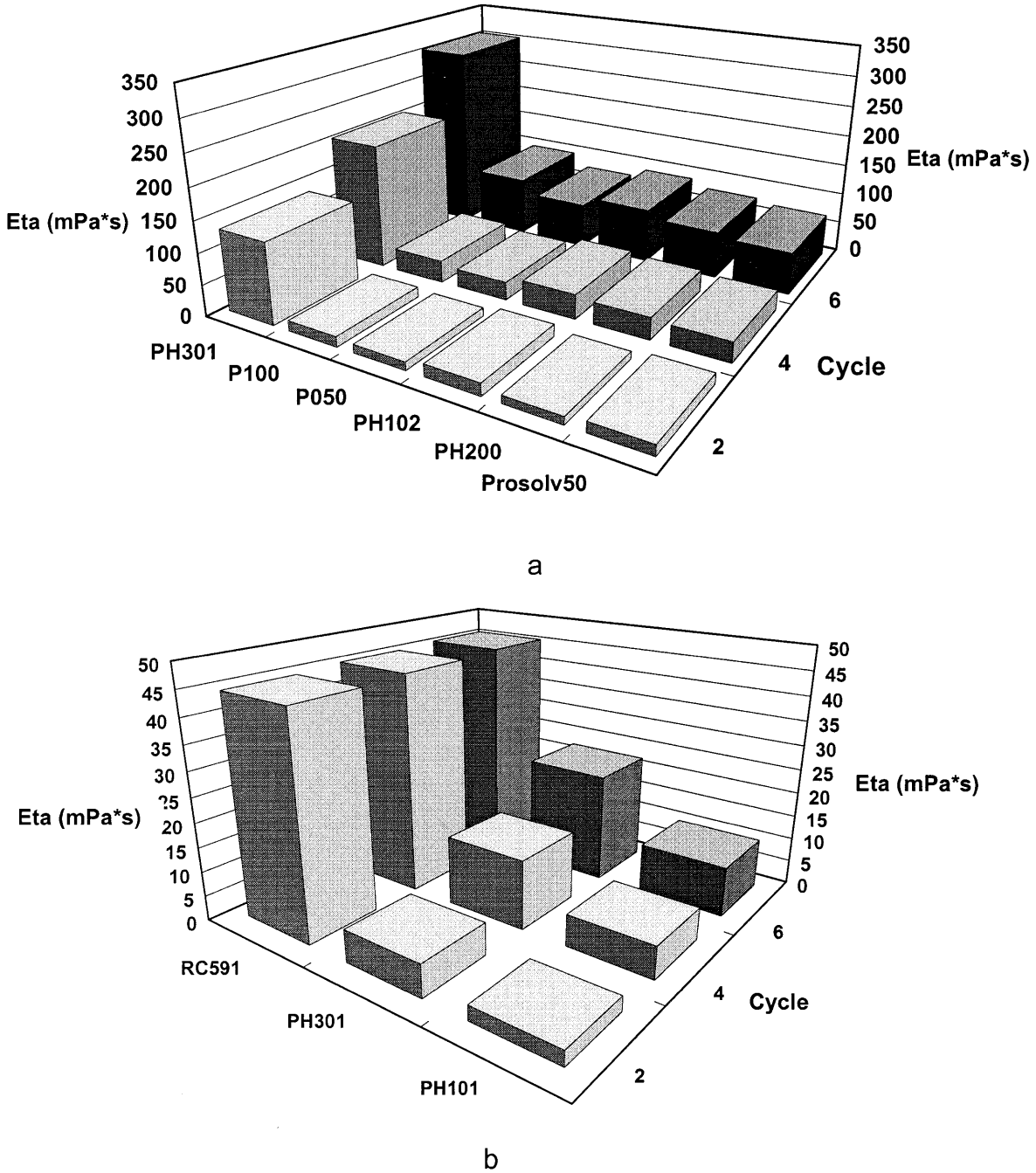
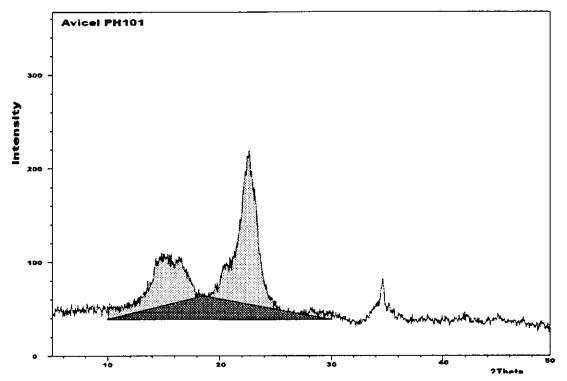


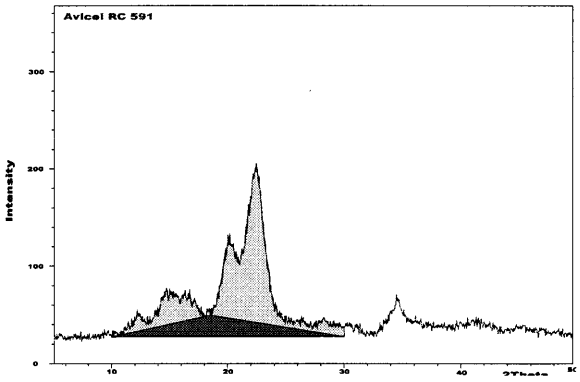
Fig. 7 Influence of the homogenisation cycles at 400 bar pressure on the viscosity (at a shear rate of 488 s^{-1}) of different MCC and PC types: **a** 9% suspension and **b** 3% suspension

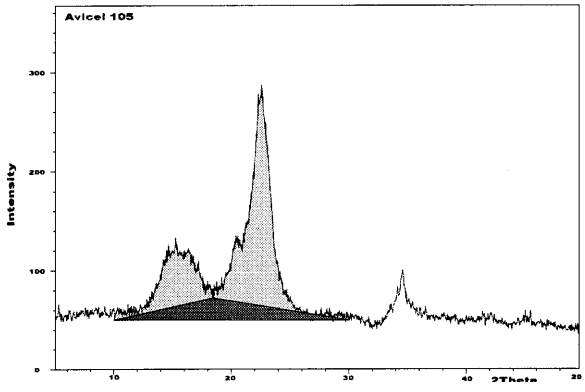
viscosity at a low concentration (3%) in comparison with PH types. This behaviour is well known for the RC type and, therefore, has been used in suitable concentrations to produce suspensions or thixotropic gels [19].

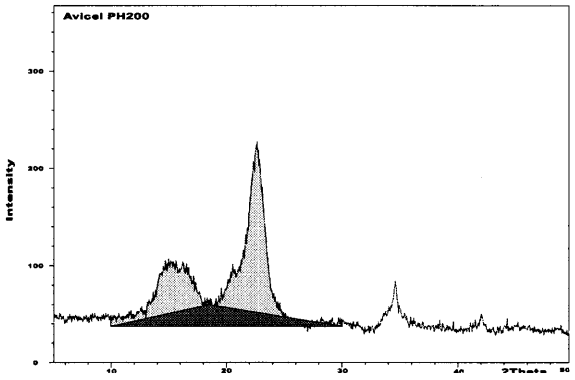
Conversely, the PC suspensions showed other behaviour. There was a negligible reduction in their particle size before as well as after the ultrasonic treatment. Furthermore, the PC suspensions had an agglomeration index close to 1, whereas the MCCs had a larger one. This means that only the MCC suspensions contained agglomerates, whereas the PCs suspensions did not.

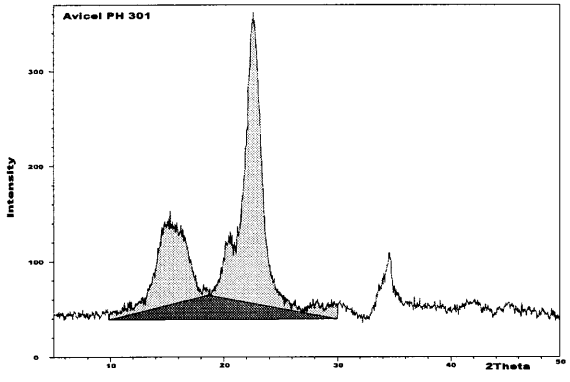
Regarding the rheological measurements, MCCs as well as PCs showed a marked increase in their viscosity after the homogenisation process; however, the PC suspensions displayed less shear-thinning behaviour

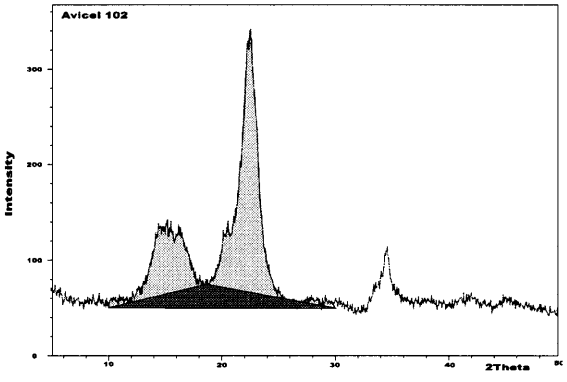

Avicel PH101
Intensity
2Theta

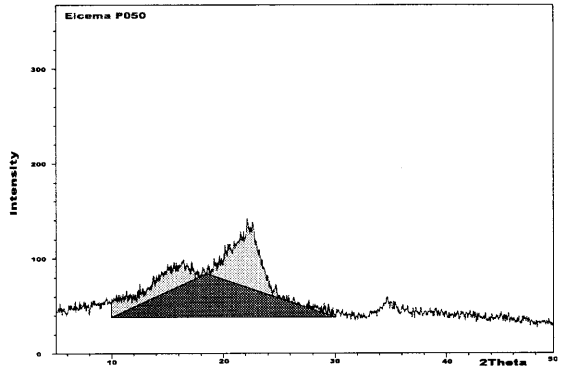

Avicel RC 591
Intensity

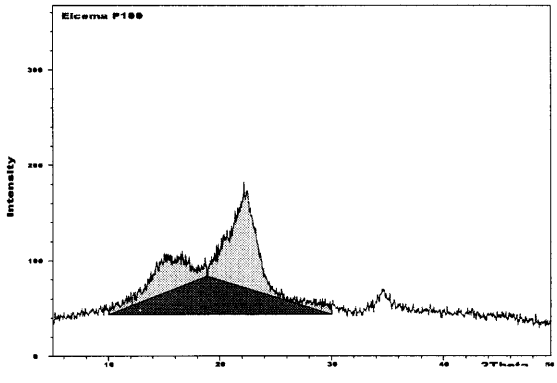

Avicel 105
Intensity
2Theta


Avicel PH200
Intensity


Avicel PH 301
Intensity
2Theta


Avicel 102
Intensity
2Theta


Eicema P050
Intensity
2Theta


Eicema P100
Intensity

◀

Fig. 8 X-ray patterns of the various cellulose types investigated

than the MCC suspensions. According to this no obvious relationship between the decrease in the particle size and the resulting viscosity could be observed. It could subsequently be concluded that the viscosity of the system is not determined by the average particle size or the particle size distribution. This is in good agreement with the reported data by Ono et al. [20], who proposed that other factors such as the shape of the MCC, the CI and the DP may also be important because a net structure formed by the MCC particles will easily change depending on such factors. Concerning the crystallinity, PCs have lower values in comparison with MCC types, whereas PH 301 and PH 102 have the highest values among the MCCs.

Taking the agglomeration indices into consideration, only MCC samples clearly showed large agglomerates accompanied by a concomitant decrease in their particle size, whereas PC suspensions did not contain agglomerates and there was a negligible reduction in their particle size, although their viscosity increased after the homogenisation process. This increase in the viscosity of the PC suspensions could, in most instances, be attributed to the great amorphous region as Suzuki and Nakagami [21] explained. They reported that the amount of water adsorbed by cellulose increased with the decrease in CI. This was caused due to the fact that the amorphous region is more hydrophilic than the crystalline region [21, 22]. Thus, PCs can absorb a large amount of water but without forming a delicate network structure because no reduction in their particle size was observed. Consequently, no new surface areas and/or no new contact points will be available and, thus, no more water could be immobilised and only a weak network was formed [23]. For this reason no agglomeration in PC suspensions was noted. This can also explain why the viscosity of the PC suspensions was less affected by increasing the rate of shear (less shear-thinning behaviour).

To summarise it could be said that homogenisation decreased the particle size of the MCCs, whereas the particle size of the PCs was not affected. The reduction in particle size led to an increase in the surface area and, consequently, more water could be immobilised. This could also be affected by the cellulose crystallinity. Thus, as a result, the amount of free water will be reduced and also the mobility of the MCCs as a consequence of the stronger interaction between the MCCs. Due to this deformation, a coherent, percolating network will be built. This network showed thixotropic rheological behaviour: it liquefies reversibly upon shaking and solidifies upon standing, with the process being time-dependent. This network should, therefore, be characterised as a gel, whereas microcrystal gels appear to be thixotropic and pseudoplastic (e.g. bentonite, colloidal silica and MCC Avicel RC).

References

1. Schröder M, Kleinebudde P (1995) Eur J Pharm Biopharm 41:382
2. Herman J, Remon JP, Visavarungroj N, Schwartz JB, Klinger GH (1988) Int J Pharm 42:15
3. Schultz P, Kleinebudde P (1997) J Controlled Release 47:191
4. Marchessault RH, Morehead FF, Koch M J (1961) J Colloid Sci 16:327
5. Dong XM, Revol JF, Gray DG (1998) Cellulose 5:19
6. Evans R, Luner P (1989) J Colloid Interface Sci 128:464
7. Ek R, Alderborn G, Nyström C (1994) Int J Pharm 111:43
8. Lindner H, Kleinebudde P (1994) J Pharm Pharmacol 46:2
9. Kleinebudde P (1997) Pharm Res 14:804
10. Ek R, Newton M (1998) Pharm Res 15:509
11. Bock T (1994) PhD thesis. University of Kiel, Germany
12. Bleich JU, Kleinebudde P, Müller BW (1994) Int J Pharm 106:77
13. Thies J, Müller BW (1998) Eur J Pharm Biopharm 45:66
14. Jumaa M, Müller BW (1998) Int J Pharm 174:29
15. Becher P (1988) Encyclopedia of emulsion technology. Dekker, New York, pp 137–222
16. Knolle H, Jayme G (1965) Das Papier 19:106
17. Brittain HG, Lewen G, Newman AW, Fiorelli K, Bogdanowich S (1993) Pharm Res 10:61
18. Rowe RC, Mckillop AG, Bray D (1994) Int J Pharm 101:169
19. Falkiewicz M (1979) Chem Spec, April:27
20. Ono H, Yamada H, Matsuda S, Okajima K, Kawamoto T, Iijima H (1998) Cellulose 5:231
21. Suzuki T, Nakagami H (1999) Eur J Pharm Biopharm 47:225
22. Ek R, Lennholm H, Davidson R, Nyström C, Ragnarsson G (1995) Int J Pharm 122:49
23. Ono H, Inamoto M, Okajima K (1997) Cellulose 4:57