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Powder and Mechanical Properties of Microcrystalline Cellulose With Different Degrees of Polymerization

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ABSTRACT This study investigated the influence of the degree of polymerization (DP) of cellulose materials (microcrystalline cellulose [MCC]) on some powder properties and the compression behavior of these materials. The DP was determined by measurements of viscosity (*H*). The weight average of molecular weight and the weight average of the different DPs were investigated after MCC was modified to cellulose tricarbanilate by light scattering measurements. The DP showed a remarkable influence on the physicochemical properties of the cellulose materials and, consequently, on the behavior of these materials during compression. MCC types with a high DP value showed greater water absorption than the types with a low DP value. No relevant relationship between the crystallinity index and the DP could be observed. DP 190 showed lower compactibility and compressibility parameters than DP 244 and 299. No significant differences could be observed between DP 244 and 299 when the same particle size fraction was compressed. Furthermore, the compressibility was increased by increasing the DP.

Key Words: microcrystalline cellulose, degree of polymerization, light scattering, cellulose tricarbanilate, compression, tablet.

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INTRODUCTION

Microcrystalline cellulose (MCC) has been widely used as an additive for direct compression because of its good flowability, compactibility, and compressibility. MCC is usually manufactured by the following process: wood pulp made of needle-leaf trees or return pulp made of cotton-seed fiber is partially hydrolyzed and washed after removing the amorphous region and impurities to purify the MCC. Therefore, it has been indicated that differences in the properties of MCC among manufacturers are due to the kinds of pulp used as a raw material and their manufacturing conditions. These differences can affect the compactibility and compressibility of the MCC. Thomas and Pourcelot [1] reported that the compactibility index differed among 5 brand-name MCCs. Several studies investigated the reason for these differences. Rowe et al [2] pointed out that the particle size of MCC affected tablet characteristics much more than the crystallinity. Pesonen and Paronen [3] concluded that the most important materials property affecting the breaking strength of tablets was the specific surface area of the used material, and no correlation between crystallinity, particle size, or particle shape of the starting material and the compactibility was observed. Ikeda et al [4] evaluated the compactibility of powder cellulose, which had a higher degree of polymerization (DP) than MCC. Suzuki and Nakagami [5] pulverized MCC to vary the crystallinity of one brand-name MCC (Avicel PH 101). They concluded that the compactibility parameters were lowered as the degree of crystallinity of MCC became smaller. Kleinebudde et al [6] reported that altering the DP resulted in great changes in the behavior of the material during the homogenization and extrusion processes. Dybowski [7] investigated the physical properties of different MCCs that had different DPs and were produced from different wood types with different DPs. The results showed that not the DP, but the origin of the raw materials and the production method decisively influence the characteristics of MCC. They produced tablets by using a constant setting of a rotary tablet machine, which resulted in different measured compression forces because of the different bulk densities of the different MCC types. In the end, tablets with different thicknesses, weights, and crushing strengths were produced.

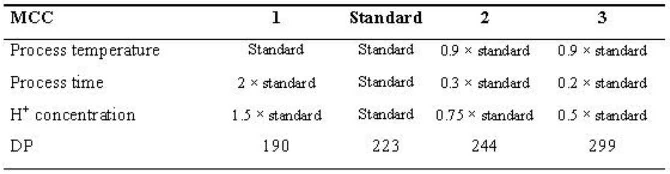
The aim of this work was the comprehensive investigation of the powder and mechanical properties of Microcrystalline Cellulose 102, produced by J. Rettenmaier & Söhne, with different DPs (190, 244, and 299). The wood source of the different MCCs is the same and has a DP of 1600. The influence of the different DPs on the compressibility was characterized using the modified Fraser-Suzuki function [8] and Heckel plots [9-10].

MATERIALS AND METHODS

Materials

Four kinds of MCC 102 with different DPs (190, 244, and 299) were produced for this purpose by J. Rettenmaier & Söhne (Weissenborn, Germany). The manufacturing was performed for all MCC trials in the same pilot plant with a patch size of about 200 kg. The cut cellulose pulp was stirred in diluted hydrochloric acid and heated to the target temperature for a defined time. Temperature and time were varied to obtain the different DPs. Table 1 shows the different production parameters, which were varied to produce the MCCs with different DPs.

Table 1. The Production Parameters of the Modified MCC (Wood Type: Needlewood, DP 1600)



MCC	1	Standard	2	3
Process temperature	Standard	Standard	0.9 × standard	0.9 × standard
Process time	2 × standard	Standard	0.3 × standard	0.2 × standard
H^+ concentration	1.5 × standard	Standard	0.75 × standard	0.5 × standard
DP	190	223	244	299

Methods

Powder properties

The DP was determined by measuring the viscosity for the harmonized pharmacopoeia regulations [11]. It has also been used for a long time as a characterization of cellulose pulp and is therefore matured and validated. For the viscosity to be measured, cellulose must be placed in a solution. For this purpose, cupriethylenediamine hydroxide solution (cuene) was used. The monograph stipulates 1.0 M cuene solution. Protective measures by means of nitrogen aeration are required in this solution because of the rapid disintegration of the solution by oxidation. The increase of viscosity is directly proportional to the DP of cellulose. Since the measurement deals with an ideally viscous liquidity (Newton's fluidity) in the solution, the viscosity was determined by using one point measurement with a capillary-type viscosimeter. The measured flow time is multiplied by the apparatus constant to a kinematic viscosity. Dividing the true by the blank value of the kinematic viscosity, the relative viscosity is obtained. Then the intrinsic viscosity—[η]*c*—is determined by interpolation using the intrinsic viscosity table. From there, the DP is calculated by the following equation:

$$DP = \frac{95[\eta]c}{m[(100-b)x10^{-2}]} \tag{1}$$

where: m is the material mass and b is the loss on drying (%).

The determination of the molecular weight distribution of the delivered MCC was done with light-scattering measurements. For this purpose, the

MCC was converted polymer-analogous into the cellulose tricarbanilate as described here. About 200 mg of dried (water-free) MCC was suspended in 10 mL of absolute pyridine in a 3-neck flask with stirrer, dropping funnel, and refluxer. Four drops of dibutylzinndidodecannate were added to the suspension as a catalyst, heated to 100°C, and stirred, and then 2 mL of phenylisocyanate was added slowly. The result was a viscous solution of cellulose tricarbanilate. After 2 hours, the reaction mixture was cooled to 50°C. An excess of phenylisocyanate was deactivated with 10 mL methanol. After that, dropping the solution into 200 mL methanol precipitated the cellulose tricarbanilate. For further purification, the precipitated cellulose tricarbanilate was stirred in 400 mL methanol for 12 hours. Then the crude product was filtered and dried in a vacuum. In a last purification step, the cellulose tricarbanilate was dissolved in dioxane. From the clear solution the product was precipitated by dropping the solution in an excess of water, filtered, once more dissolved in dioxane, precipitated in water, filtered, and dried. This method was described in detail by Buchard [12]. The reason for this polymer-analogous reaction is the solvent behavior of pure MCC. It is associated in polar solvents and the determined molecular weight is then only an apparent molecular weight.

For determination of the molecular weight distribution and the weight average of molecular weight, the cellulose tricarbanilate was dissolved in tetrahydrofuran and stabilized with 2,6-ditert-dibutyl-4-methylphenol at room temperature. Measurements for all samples were performed on a modular SEC (Size Exclusion Chromatography) apparatus equipped with a concentration (Wyatt Optilab DSP, Santa Barbara, CA) and a multi-angle light-scattering detector (Wyatt DAWN DSP-F). An HMW6E column (Waters GmbH, Esborn, Germany) was used for separation. All measurements were done with a flow of the eluant tetrahydrofurane (stabilized) of 0.8 mL/minute at room temperature. The injection volume was 100 µL, and the total concentration of the samples was about 1 mg/mL. Calculations of the light-scattering data were performed with the software Astra 4.70 (Wyatt Optilab DSP, Santa Barbara, CA). The chemical structures of MCC and cellulose tricarbanilate are shown in Figure 1.

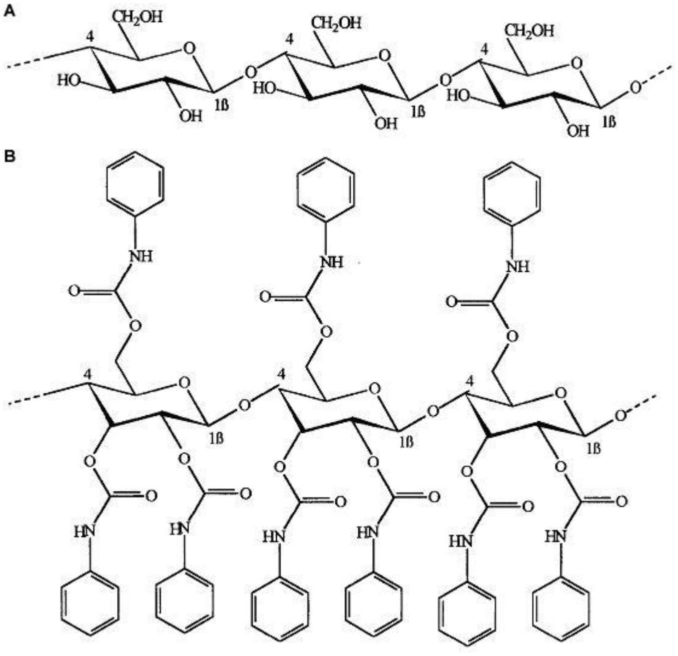


Figure 1. Chemical structure of (A) MCC and (B) cellulose tricarbanilate.

To prove the effectiveness of the chemical modification, the MCC and the cellulose tricarbanilate were characterized by using solid-state NMR (Nuclear Magnetic Resonance) INOVA-Type (Varian Inco. CA-USA) with a spectrometer frequency of 400 MHz.

The Hausner ratio was determined as the ratio of tap and bulk density [11]. The true density was measured by using Helium Gas Pyknometer Accu Pyc 1330 (Micromeritics Instrument Corp, Norcross, GA-USA) Details about this method are provided by Shlieout [13].

The water absorption was measured by using a modified van Kamp water absorption apparatus(MLU-Halle Germany) [14]. In this apparatus, the mass lost of the water is measured by using a digital balance (Satorius LC 200, Satorius AG, Göttingen-Germany). The data were evaluated by using an internal evaluation program described in detail by Shlieout [13].

The particle size distribution was measured by using a laser diffraction analyzer (PS 2600) and a dry dispersion unit PS 64, Malvern Instrument, Malvern, England. A beam expander of 10 mm and a 300-mm lens were used. Three measurements were made for each MCC type. The powders were characterized by the d50 and d90 quantiles of the volumetric distribution. The mean diameter, d50, is defined as the size at which 50% of the particles are smaller; d90 is defined as the size at which 90% of the particles are smaller. Furthermore, the fine part (< 34 µm) was characterized by adding the powder amount (%), which is smaller than 34 µm.

The fractionation was done by using an air jet sieve (Hosokawa, Alpine 200LS-N, Osaka, Japan) with standard sieves.

To characterize the flowability, the mean flow rate (g/s) of the powder was determined: a steel funnel [11] was used, and a computer-connected balance continuously registered the mass of the powder. A 50-Hz vibrator was connected with the funnel to improve the powder flow. The mean flow rate was evaluated by linear regression.

The specific surface area (m^2/g) was determined by nitrogen adsorption isotherm (Quantasorb; Quantachrom GmbH, Odelzhausen, Germany).

In the scanning electron microscopy, the powder particles were evaporated with carbon and then sputtered with gold to connect the samples electrically. The sputter apparatus was SCD 050 (Balzers Union AG, Vaduz, Liechtenstein). The vacuum was 5×10^{-2} mbar, and the layer thickness was carbon app. 10 nm, gold approximately 25 nm, scanning electron microscope S-2400 (Hitachi, Tokyo Japan).

The degree of crystallinity was determined using an x-ray powder diffractometer (PW3710; Philips Industrial Electronics Deutschland GmbH, Kassel, Germany), and the crystallinity index was evaluated according to Knolle and Jayme [15].

Production of the tablets

An instrumented single-punch machine was used (EK0/DMS No. 1.0083.92, Korsch GmbH, Berlin, Germany). The upper-punch and lower-punch forces were measured. The displacement of the upper punch was measured by using an inductive transducer (W 20 TK, Höttinger Baldwin Meßtechnik, Darmstadt, Germany). The measured displacement of the upper punch was not exactly correct because of the elastic deformation factors of the different parts of the tablet machine, which cannot be detected from the displacement sensor. These factors were evaluated to measure the correct displacement value. Details about the determination of the elastic deformation of the tablet machine can be found in Shlieout et al. [8]. The calibration of the transducer was done by using steel slip gauges of 2, 3, 4, and 5 mm height. The tablet machine is connected with DMC-plus amplifier (Höttinger Baldwin Meßtechnick, Darmstadt, Germany). The materials were compressed with flat circular punches of 9-mm diameter at a rate of 10 tablets/minute. The materials were compressed without any other excipients to different compression forces and porosities. The evaluation of the porosity was done during the compression cycle according to the following equation:

$$Porosity = \left(1 - \frac{\rho_{maz}}{\rho_{true}}\right) x100 \qquad (2)$$

where: ρ_{max} = tablet bulk density by upper-punch displacement maximum under load and ρ_{true} = true density of the compressed material

The diametrical crushing strength was tested using an Erweka strength tester TBH-28 (Erweka GmbH, Offenbach, Germany). The mean value of 10 determinations was reported.

To characterize the compressibility, the modified Fraser-Suzuki function can be used as a fitting function for the force-time course and gives 3 parameters, which can describe the reversible and irreversible deformation behavior of the compressed material [8]:

$$f(t) = H \times \exp\left\{\left[\frac{-0.693}{A^2}\right] \times \left[\ln\left(\frac{\langle 1 + A \times (tr - t)\rangle}{S}\right) \times 1.177\right]^2\right\} \quad (3)$$

where H is the compression force maximum, A and tr give information about the irreversible deformation, and S provides information about the reversible deformation. Furthermore, the k parameter of the Heckel equation was used, which has an indirect proportional relationship to the yield strength.

RESULTS AND DISCUSSION

Powder properties

The powder properties of the different DPs are summarized in Table 2. The bulk and tap density decreased, and so the Hausner factor values increased by increasing the DP. The flowability decreased by increasing the DP, which can be established with the fiber form of the particles. The specific surface area was increased by increasing the DP.

Table 2. Powder Properties for Each DP

	DP 190	DP 244	DP 299
Bulk density (g/cm^3)	0.445	0.2055	0.167
Tap density (g/cm^3)	0.607	0.346	0.307
Hausner factor	1.36	1.77	1.84
Specific surface area (m^2/g)	0.824 ± 0.016	1.212 ± 0.012	1.221 ± 0.01
Crystallinity index (%)	65.56	65.77	66.78
Flowability (g/s)	4.7	2.1	0.7

The reason for these differences involves the structure and morphology of the different DPs, as can be seen in Figure 2. The scanning microscopy pictures show that the particles of DP 190 have an irregular round shape with a porous surface (Figure 2A). DP 244 and 299 (Figure 2B, 2C) show almost the same fiber particle shape; the surface of the fibers gets smoother as the DP increases. Furthermore, the fibers are relatively adhesive, which explains the bad flowability compared with DP 190 (Table 2).

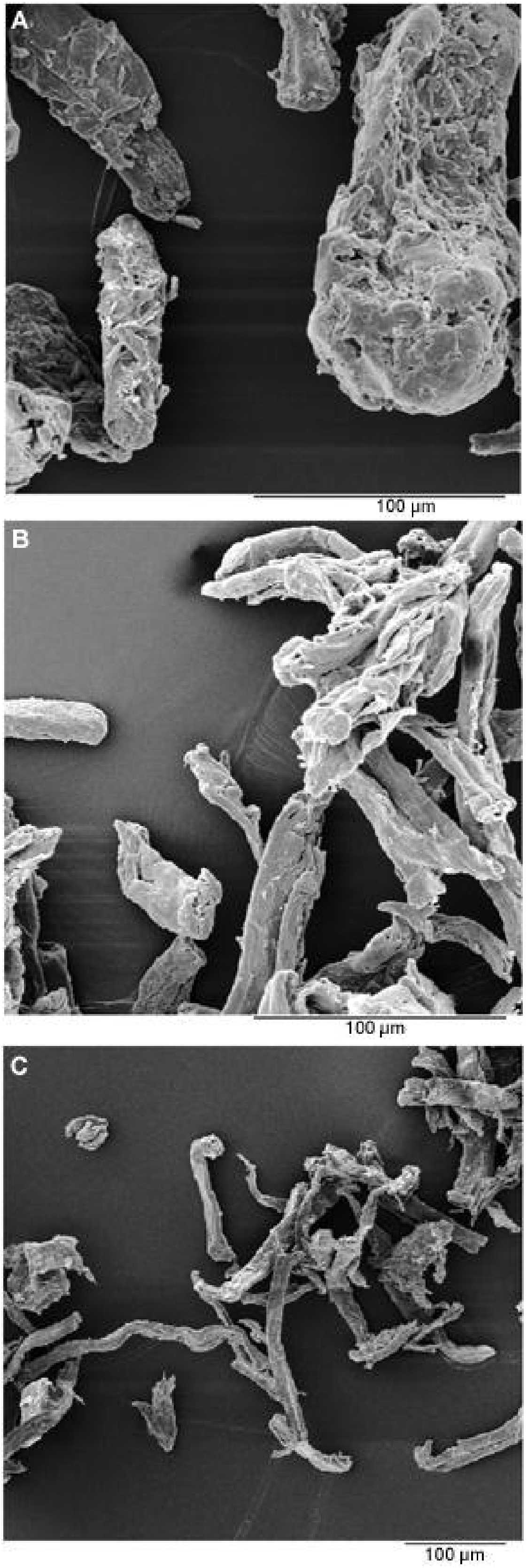


Figure 2. Morphology for (A) DP 190, (B) DP 244, and (C) DP 299.

The results clearly show that the DP decisively influences the characteristics of microcrystalline cellulose. Plotting the particle size (D50 and D90) of the cellulose against the DP value (Figure 3) clearly shows that there is no correlation between the particle size or fine part (< 34 µm) and the DP values of the different MCCs. Kleinebudde et al [6] found a significant correlation, with a proportional relationship, between the suspension particle sizes and the DP values of different MCCs. This difference between our results and the results of Kleinebudde et al [6] is due to the water absorption that occurred in the suspension medium. Furthermore, our results show that the fine part does not correlate with the DP values.

DP 190 has the largest d50 and d90 and the lowest fine part. DP 244 and DP 299 have a lower fine part compared with DP 190, which could partly affect the compression behavior of the different MCC types.

A proportional relationship between water absorption and DP of MCC could be found. The reason for this behavior is probably the higher molecular weight, which can bind more water molecules. Figure 4 shows the water absorption for the different MCCs. A t test showed that the values were significantly different. By increasing the DP (i.e., the molecular weight), an increase in the water binding positions can be achieved, which probably explains the water absorption behavior of the different DPs.

The same behavior was found by investigation of ethylcellulose with different molecular weight (i.e., viscosity) in a 5% solution [13]. Ethylcellulose 50cP showed higher water absorption than ethylcellulose 7cP.

The evaluation of the crystallinity index according to Knolle and Jayme shows that the different DPs do not have significantly different values (Table 2).

The intrinsic viscosity is related to the DP, but if the molecular weight distribution of the polymer is bi- or trimodal the relationship between DP and [h] is not the same as in the case of a unimodal distribution. For this reason, we decided to determine the molecular weight distribution.

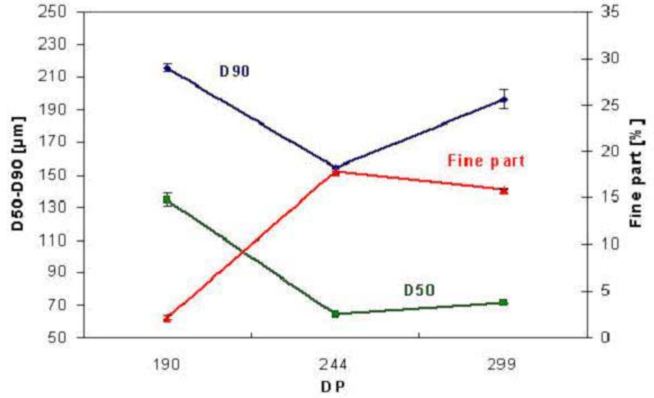


Figure 3. Correlation between DPs and d_{50}, d_{90}, and fine part.

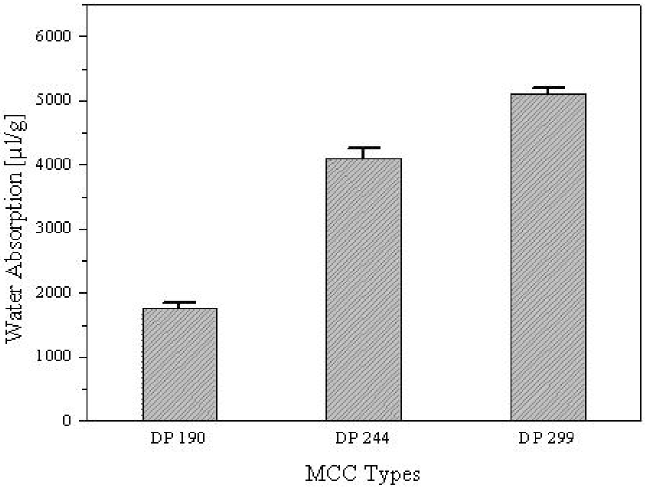


Figure 4. Water absorption for each DP.

To characterize the molecular weight distribution, the investigated celluloses were modified to cellulose tricarbanilate, as mentioned before. The investigation shows that all celluloses have a unimodal molecular weight distribution (Figure 5) and correlate with the DP with a correlation coefficient of $R = 0.953$.

Tablet properties

The investigation of the compactability shows that the crushing strength of the tablets increases by increasing the DP (Figure 6). An increase in the DP leads to an increase in the hardness of the MCC tablets. There was a large difference between DP

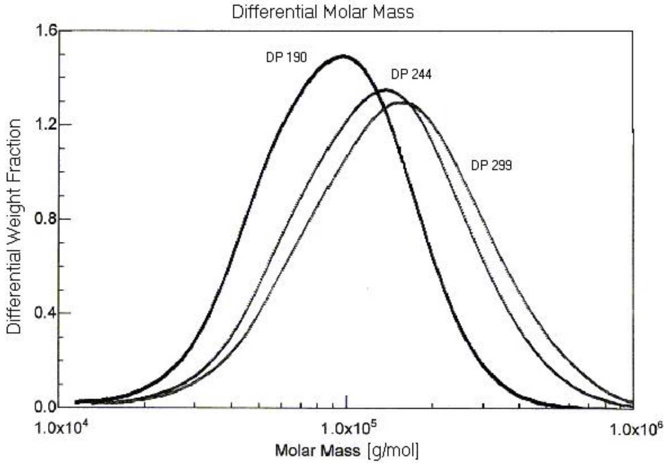


Figure 5. Molecular weight distributions of MCC with different DPs.

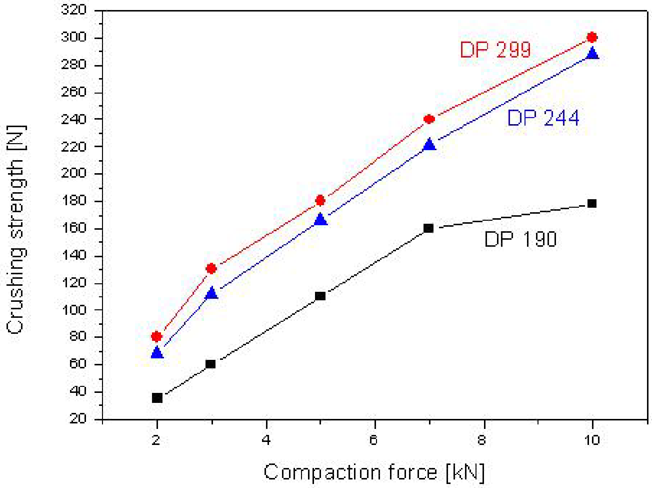


Figure 6. The crushing strength of MCC tablets with different DPs.

190 and 244 but a small difference between DP 244 and 299. These results correlate with the powder properties of the different MCCs. DP 190 has a higher mean particle size and lower fine parts, which could explain the low tablet hardness compared with DP 244 and 299. To eliminate the influence of the particle size and the fine part, the different MCCs were fractionated and the same fraction of each type (> 75 μm and < 125 μm) was compressed. As shown in Figure 7, the hardness of DP 190 is still clearly the lowest, and the difference between DP 244 and DP 299 is not significant anymore.

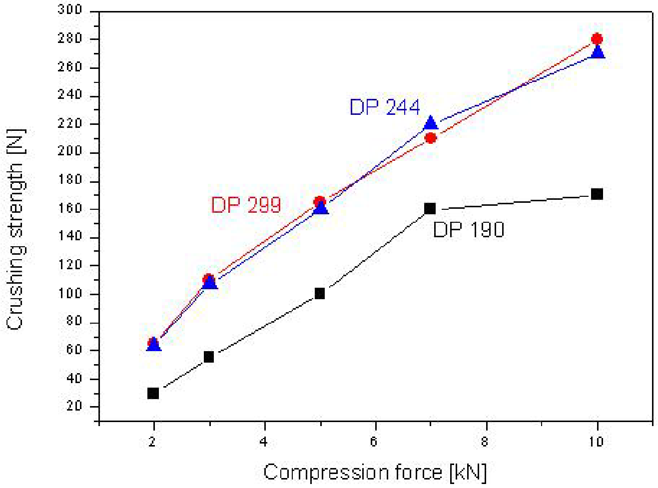


Figure 7. The crushing strength of MCC tablets with different DPs of the same fraction of > 75 and < 125 (standard deviation is smaller than the symbols).

The MCC particles of DP 244 and 299, as can be seen in Figure 2, consist of agglomerations of small

MCC particles or fibers, which can undergo fragmentation during compression. This leads to an increase of the secondary binding points, which results in tablets with high crushing strength.

It can be assumed that besides the powder properties of the different DPs, the DP plays an important role in the mechanical properties of the MCC. The compression behavior of DP 244 and DP 299 correlates with the result of Rowe et al [2] that the hardness of the MCC tablets depends on the powder properties. The friability data of the MCCs with different DPs show the same behavior as the data on crushing strength (Figure 8).

The investigation of the consolidation behavior shows almost the same results as the compactability. Figure 9 shows the values of the parameter tr of the modified Fraser-Suzuki function, which correlates with the irreversible deformation. The different MCC types were compressed to different porosities. Significant differences between the MCC types (DP 190, 244, and 299) could be seen. A pronounced difference can be seen only between DP 190 and the other DPs (244, 299).

Increasing the DP decreased the elastic deformation behavior of the different MCC types. The values of

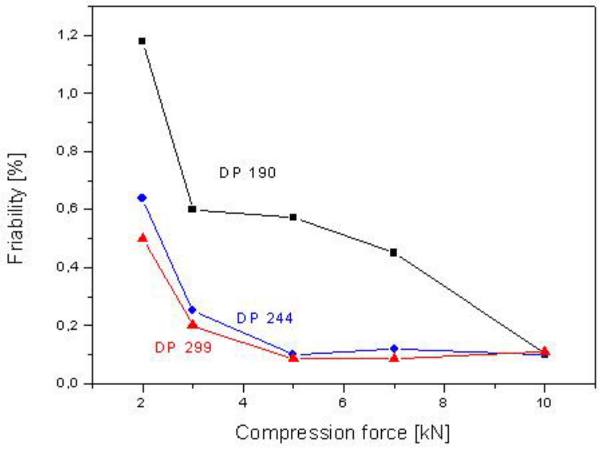


Figure 8. Friability of MCC tablets with different DPs.

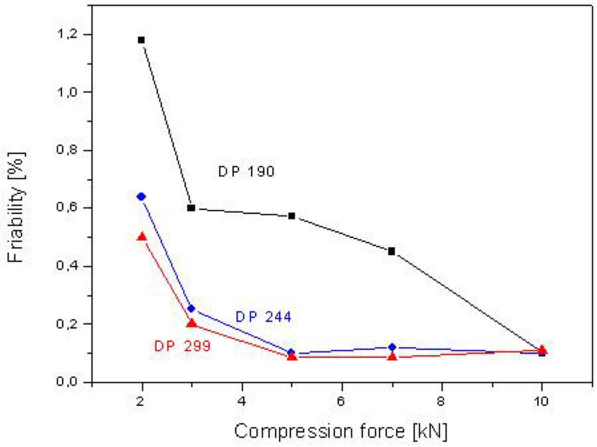


Figure 9. The values of parameter *tr* by compression of MCC with different DPs to different porosity.

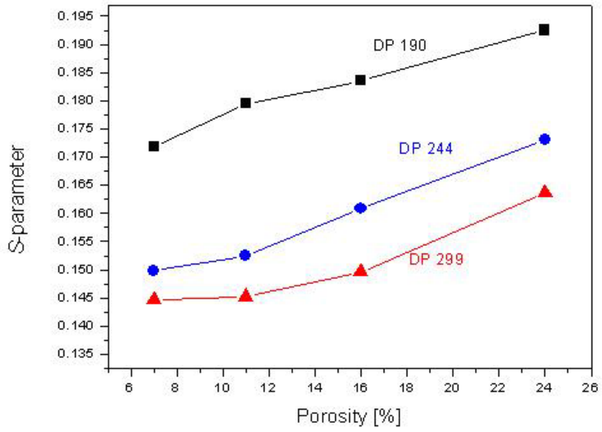


Figure 10. The values of parameter *S* by compression of MCC with different DPs to different porosity.

the S parameter of the modified Fraser-Suzuki function can be seen in Figure 10.

The elastic deformation was clearly highest for DP 190. The difference between DP 190 and the other DPs was more pronounced than between DP 244 and 299. This could be due to the better consolidation behavior of DP 244 and 299, which allowed the particles to get much closer than was possible in DP 190.

The deformation behavior of the different MCCs was also investigated by using the Heckel equation as a classical method. The results deliver qualitatively the same results as the modified Fraser-Suzuki function

In Figure 11, the *k* parameters of the Heckel equation can be seen. The lower *k* values of DP 190 reflect the lower deformation tendency of the material compared with DP 244 and 299. No significant differences could be observed between DP 244 and DP 299. Pesonen and Paronen [16] observed during the investigation of the compression behavior of MCC and agglomerated powder cellulose (APC) that APC was slightly more inclined to permanent deformation than MCC. They postulated that the possible reason for the difference in deformation behavior could be APC's more amorphous structure. Thus, there could be more lattice defects in the structure of APC, accounting for the better deformation properties. This explanation could not be confirmed in our study, because the crystallinity indices of all MCC types were similar. Duberg and Nyström [17] presented a theory concerning the volume reduction of pharmaceutical materials, which consist of aggregate of primary particles. In this theory they explain that during the initial loading, the secondary particles could behave mainly as brittle units, with slight ability to plastic deformation. After initial fragmentation, the formed primary particles would, when compression pressure was increased, deform plastically. This theory seems to apply well to the behavior of DP 244 and 299. These MCC types consist of porous agglomerates of small MCC particles (i.e., fibers), resulting in high specific surface area. It is quite possible that these agglomerates underwent fragmentation at low compressional pressure, thus forming smaller plastically deformable MCC particles. As shown in Figure 11, the *k* values increased by increasing the compression force, which is due to prolonging the time available for deformation [18].

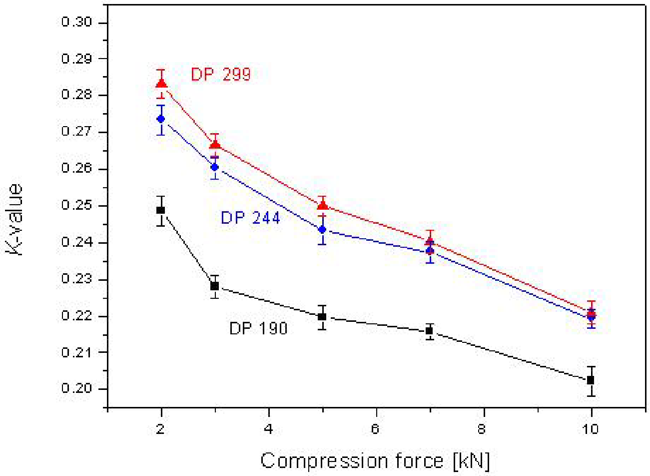


Figure 11. The values of *k* parameter of the Heckel equation by compression of the different MCC types to different compression forces.

CONCLUSION

The variation of the MCC production parameters has a significant influence on the DP (i.e., molecular weight) of the produced MCC and finally on the physical and mechanical properties of the powder. In this study a correlation between DP and compactability and compressibility could be found. The compactability parameters were lowered as the DP lowered. No significant differences were found between DP 244 and DP 299 when the same powder fractions were compressed. MCCs with higher fine part and specific surface areas led to tablets with higher crushing strengths. In contrast to previous studies, this study found that the crystallinity does not have a primary influence on the mechanical properties of the produced tablets. This study's results make the determination of the DP indispensable in order to guarantee reproducibility during the production of tablets containing MCC.

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REFERENCES

1. Thomas C, Pourcelot Y. Performulation of five commercial celluloses in drug development: rheological and mechanical behavior. Drug Dev Ind Pharm. 1993;19:194-196.

2. Rowe RC, McKillop AG, Bray D. The effect of batch and source variation on the crystallinity of microcrystalline cellulose. Int J Pharm. 1994;101:169-172.

3. Pesonen T, Paronen P. Evaluation of a new cellulose material as binding agent for direct compression of tablets. Drug Dev Ind Pharm. 1986;12:2091-2111.

4. Iieda K, Aoki K, Danjo K, Otsuka A, Chen C. Y, Horisawa E. A comparative evaluation of the mechanical properties of various celluloses. Chem Pharm Bull. 1997;45:217-220.

5. Suzuki T, Nakagami H. Effect of crystallinity of microcrystalline cellulose on the compactability and dissolution of tablets. Eur J Pharm. 1999;47:225-230.

6. Kleinebudde P, Jumaa M, El Saleh F. Influence of the degree of polymerization on the behavior of cellulose during homogenization and extrusion/spheronization. AAPS PharmSci. 2000;2(3):article 21.

7. Dybowski U. The influence of the degree of polymerization on properties of microcrystalline cellulose. Manufactur Chem. 1997;68:19-21.

8. Shlieout G, Wiese M, Zessin G. A new method to evaluate the consolidation behavior of pharmaceutical materials by using the modified Fraser-Suzuki function. Drug Dev Ind Pharm. 1999;25:29-36.

9. Heckel RW. Density-pressure relationships in powder compaction. Trans Metall Soc AIME. 1961;221:671-675.

10. Heckel RW. Analysis of powder compaction phenomena. Trans Metall Soc AIME. 1961;221:1001-1008.

11. European Pharmacopoeia. 3rd ed. Stuttgart, Germany: Deutscher Apotheker Verlag; 1997.

12. Buchard W. Über die Abweichungen von der idealen Knäulstatistik bei Amylose- und Cellulosetricarbanilat. Die Makromolekulare Chemie 1965;88:511-528.

13. Shlieout G. [PhD dissertation]. Halle, Germany: Martin Luther University; 1996.

14. Van Kamp HV, Bolhuis GK, DeBoer AH, Lerk CF, Lie AH. Role of water uptake on tablet disintegration: design of an improved method for penetration measurements. Pharm Acta Helv. 1986;61(1):22-29.

15. Knolle H, Jayme G. Über ein digitales Verfahren zur empirischen Bestimmung der Röntgenkristallinität cellulosehaltiger Stoffe und seine Anwendung. Das Papier. 1965;19:106-110.

16. Pesonen T, Paronen P. Compressional behaviour of an agglomerated cellulose powder. Drug Dev Ind Pharm. 1990;16(4):591-612.

17. Duberg M, Nyström C. Studies on direct compression of tablets; XVII: porosity-pressure curves characterization of volume reduction mechanisms in powder compression. Powder Technol. 1986;46:67-75.

18. Rees JE, Rue PJ. Time-dependent deformation of some direct compression excipients. J Pharm Pharmacol. 1978;30:601-607.