

Interaction of Microcrystalline Cellulose and Water in Granules Prepared by a High-Shear Mixer

Tatsuya SUZUKI,*^a Hiroshi KIKUCHI,^b Etsuo YONEMOCHI,^c Katsuhide TERADA,^c and Keiji YAMAMOTO^d

Pharmaceutical Technology Research Laboratories,^a and Drug Metabolism and Physicochemical Property Research Laboratory,^b Daiichi Pharmaceutical Co., Ltd., 16–13, Kita-Kasai 1-Chome, Edogawa-ku, Tokyo 134–8630, Japan, School of Pharmaceutical Sciences, Toho University,^c 2–2–1 Miyama, Funabashi, Chiba 274–8510, Japan, and Faculty of Pharmaceutical Sciences, Chiba University,^d 1–33 Yayoicho, Inage-ku, Chiba 263–8522, Japan.

Received September 11, 2000; accepted December 20, 2000

Microcrystalline cellulose (MCC) granules were prepared by wet granulation using a high-shear mixer. Physical characteristics of the granules were investigated using near IR spectrometry, thermogravimetry and isothermal water vapor adsorption. Near IR spectra of dried MCC granules prepared for various granulation times exhibited different peak intensities at 1428, 1772, and 1920 nm, which were assigned to functional groups of cellulose or water. On isothermogravimetric analysis, the rate of dehydration of water was shown to decrease with granulation time. These results suggest that the physical structure of MCC could change during the granulation process, and the interaction between MCC and water was gradually strengthened. The isothermal water vapor adsorption curves suggested that the amorphous region of MCC would be divided by the strong shear force of the impeller, because the high adsorption ability of intact MCC in the low humidity region was diminished in granules collected following 5 and 10 min of granulation. It was suggested that MCC formed a network which caught water within its structure during the wet granulation process.

Key words microcrystalline cellulose; granulation; near IR; water

Microcrystalline cellulose (MCC) is frequently used in the manufacture of pharmaceutical products, as a binder for tablets and as a granulation aid in extrusion or wet granulation by a high-shear mixer.^{1–5)} Two models have been proposed for the role of MCC in wet granulation: the ‘sponge model’ proposed by Fielden *et al.*,⁶⁾ and the ‘crystallite-gel model’ proposed by Kleinebudde.⁷⁾ No conclusion has yet been reached regarding which model is correct.⁸⁾ In the ‘sponge model’, MCC is considered to be a porous sponge due to its high water absorption capacity. That is, a portion of the water held in the MCC is squeezed out when pressure is applied by an extruder. When the pressure is removed, MCC can again absorb water and recovers its original shape and size. On the other hand, in the ‘crystallite-gel model’, MCC is divided into small particles by the strong shear force of an impeller, and ultimately forms crystallites. Then, small particles form a network due to entanglement with each other.

We sought to clarify the role of MCC in the increasing hardness of granules in wet granulation by a high-shear mixer to determine the granule physical structure using the X-ray small angle scattering method and wide angle X-ray diffraction method.⁹⁾ We speculated that the fibril chain in MCC would be divided, and that it formed a network structure during the granulation process, in the same way as in the ‘crystallite-gel model’. MCC particles in MCC granules had a different shape and reduced size as compared with the original particles, and we reported that the specific surface area of MCC was reduced compared with that of intact MCC. In this study, we reinforced our reasoning by examining the changes in the interaction between MCC and water.

Many studies have referred to the interaction between MCC and water.^{10–12)} In recent years, near IR spectrometry has been used to investigate the state of water in polymer substances. Water is one of the most troublesome solvents in IR spectrometry due to its strong bands. In near IR spectrometry, however, quantitative analysis can be performed in the

presence of water, because water shows only moderate peak strength and does not disturb the detection of peaks from other components. Therefore, it is possible to estimate organic compounds even in the solution state or under conditions of high moisture content. Moreover, water itself can become an object of study in the near IR method. Buckton *et al.* analyzed the first overtone assigned to stretching the vibration of water, and detected the transition of the crystal state of lactose using near IR without disruption of samples.¹³⁾ Moreover, using the near IR method, they clarified that MCC granules and silicified MCC granules, both of which were prepared by wet granulation, have different physical structures.¹⁴⁾

The objective of this study was to investigate the state of water in MCC granules and to explain the changes in the physical characteristics of MCC during the granulation process using thermogravimetry and isothermal water vapor adsorption in addition to near IR spectrometry.

Experimental

Materials MCC (Avicel PH101) was purchased from Asahi Chemical Industry Co., Ltd., Japan. Purified water was used as the granulating fluid.

Analytical Apparatus The average particle size of dried granules was measured using GRANO (Okada Seiko Co., Ltd., Japan), which can detect the particle diameter using a small chip connected to a load cell. The diameters of twenty dried granules were measured.

Moisture contents of the dried granules were determined by the Karl Fisher method (Metrohm 719, METROHM, Switzerland).

Near IR spectra were measured using a Rapid Contact Analyzer (NIRSystems 6500 spectrometer, NIRSystems, U.S.A.). Granules in the fraction between 30- to 42-mesh were used. Two grams of granules were weighed, and put them into a transparent glass container, and then each glass container was tapped 20 times in order to make the filling state uniform. Samples in these tightly closed glass containers were placed on the equipment and absorbance was determined in the range of 1100–2500 nm. The spectra were expressed as averages of 32 scans per sample. These measurements were repeated five times to ascertain the repeatability of measurements.

Samples of dried granules (typically 7 mg) were placed in the pan of a thermogravimetry analyzer, TGA-7 (PerkinElmer, Inc., U.S.A.) and heated from room temperature at 2 °C/min up to 30 °C, and then the changes in the

* To whom correspondence should be addressed. e-mail: suzuk87c@daiichipharm.co.jp

sample weight were measured at 30 °C for 30 min.

The equilibrium moisture curves were measured at 25 °C with an Integrated Microbalance System, MB 300G (VTI Corporation, U.S.A.).

Sample Preparation Granulation was carried out with a High Speed Mixer FS-GS-1 (Fukae Powtec, Japan), which was equipped with a 3-blade main impeller. The rotation speed of the main impeller was maintained at 500 rpm, and the chopper was not used. Granulation was performed with 100 g of MCC and 100 ml of water. Samples were withdrawn at 1, 5, and 10 min after addition of water. The damp mass sample was put into a transparent glass bottle tightly sealed with a metal cap, and preserved as wet granules at room temperature until the estimations were made. The damp mass was sampled separately at the same time and dried in a tray dryer at 50 °C for 8 h, then stored at 25 °C and 60% relative humidity to maintain the moisture content in dried granules between 5 and 6%. Dried samples were sieved through 30- and 42-mesh screens, and the fraction between 30- and 42-mesh was used for evaluation.

Results and Discussion

The average particle diameters of dried MCC granules are shown in Table 1, and the moisture content is shown in Table 2. All dried granules exhibited almost the same moisture content as intact MCC.

Electromagnetic waves between about 800 to 2500 nm in length are called near IR in general. All absorption in the near IR region takes place due to overtone or combination vibrations. Most absorptions occur by functional groups of O–H, N–H, and C–H, which are participated in by hydrogen atom. Vibrations consist of stretching and deformation, and the irradiated beam is spent as vibration energy and rotational energy of molecule in excited state. A molecule consisting of two atoms exhibits an absorption due only to stretching as a basic vibration. In the case of a molecule consisting of more than three atoms, deformations occur in addition to stretching. If an absorption based on basic vibration appears in the middle IR region, absorption appears at wavelengths of integral multiples of basic vibration in the near IR region. Qualitative and quantitative analysis can be carried out by analyzing these absorptions. In near IR spectrometry, the degree of absorption is weaker than absorption obtained in the middle IR region, therefore determination can be performed without dilution or destruction of the sample.

Near IR spectra of wet granules and dried granules are shown in Figs. 1 and 2, respectively, compared with those of

intact MCC. Near IR spectra of wet MCC granules were different from that of intact MCC, although those of dried MCC granules were similar to that of intact MCC. The second derivatives of near IR spectra were compared to investigate the wavelength and the intensity of the peaks in detail.

Figure 3 shows the relationship among original curve, first derivative and second derivative. In the first derivative, the peak in the original curve becomes zero and inflection points exist at both sides of the original curve appear as positive and negative peaks in the first derivative. In the second derivative, though the sign of the positive or negative peak is inverted in comparison to the original curve, the wavelength of the peak corresponds to that in the original curves. The second derivative has the following advantages; 1) it makes peak detection easy, because an original peak which is difficult to determine due to broadness becomes sharp, 2) it separates overlapped peaks from single peaks, and 3) it corrects the background.

The second derivatives of wet MCC granules compared with that of intact MCC are shown in Fig. 4. The second derivatives of absorbance obtained from wet MCC granules collected at 1, 5, and 10 min of granulation time revealed almost the same intensities at the same wavelength, and near IR spectra patterns did not depend on the granulation time.

Table 1. Mean Particle Diameter of Dried MCC Granules Used for Measurements

Granulation time (min)	Mean particle diameter \pm S.D. (μ m)
1	411 \pm 31
5	405 \pm 35
10	412 \pm 38

Table 2. Moisture Content of Intact MCC and Dried MCC Granules

Sample	Moisture content (%)
Intact MCC	5.87
MCC granulated for 1 min	5.51
MCC granulated for 5 min	5.56
MCC granulated for 10 min	5.23

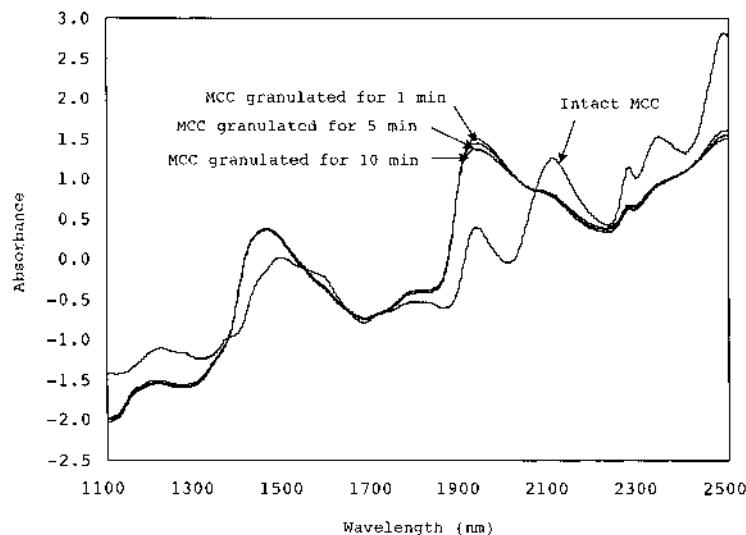


Fig. 1. Near IR Spectra of Intact MCC and Wet MCC Granules

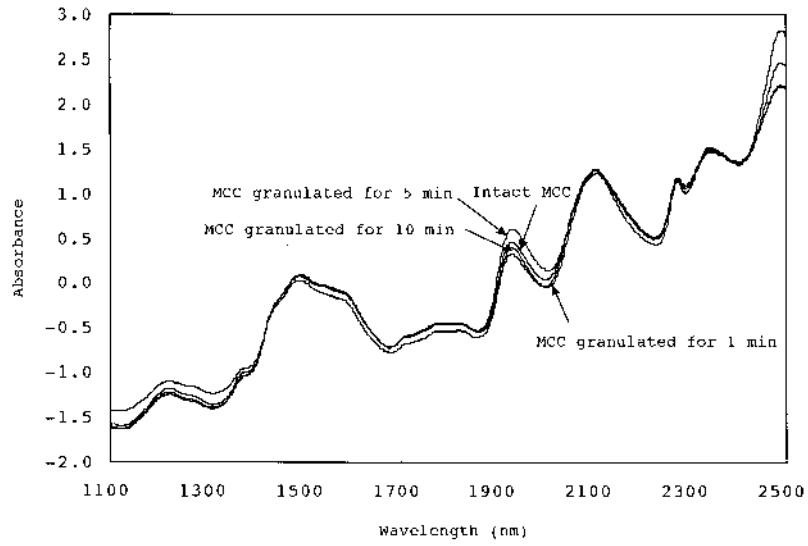


Fig. 2. Near IR Spectra of Intact MCC and Dried MCC Granules

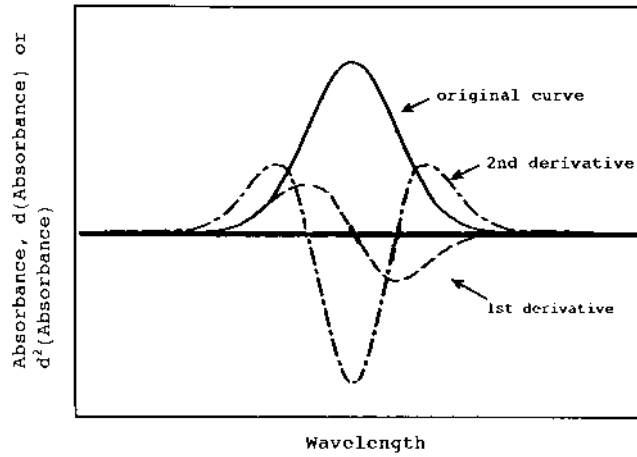


Fig. 3. Relationship between Original Curve and Its Derivatives in Near IR

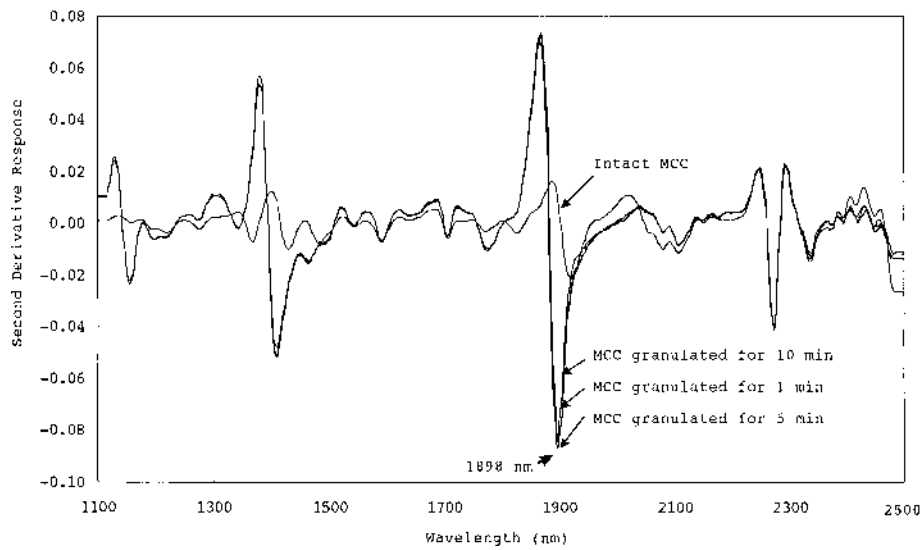


Fig. 4. The Second Derivatives of Spectra for Intact MCC and Wet MCC Granules

These results suggested that it would be difficult to distinguish the differences in the interaction between MCC and water in the wet state, because water contents in samples were too high. The absorption band centered at 1898 nm, which was the greatest peak in the spectra of the wet MCC granules, was assigned to O–H stretching vibration of bulk water molecules.^{15,16} This suggested that free water molecules, which interact little with MCC, were present in the wet MCC granules.

The second derivatives of near IR spectra for dried MCC granules and intact MCC are shown in Fig. 5. The assignments of absorption band were as follows: 1482 nm, first overtone of O–H stretching vibration, which forms an intramolecular hydrogen bond in cellulose; 1772 nm, first overtone of C–H stretching vibration in cellulose; 1920 nm, the combination of O–H stretching and deformation vibration of water molecules.^{15,16}

The relationships between the second derivative peak height and granulation time are shown in Figs. 6 and 7. As the standard deviations of the second derivative peak height in all points were no less than 0.05%, measurement was believed to be highly reproducible. The absolute value of the

second derivative peak height derived from the mobility of cellulose molecules at wavelengths of 1482 and 1772 nm increased with granulation time (Fig. 6). Although the height of the peak assigned to the mobility of water molecules also increased with granulation time up to 5 min, almost the same peak heights were recognized in dried MCC granules granulated for 5 and 10 min (Fig. 7). However, the value of the second response will differ due to equipment used or granulating conditions such as rotating speed, the quantity of water or brand of MCC and so forth.

The results of this experiment suggested that MCC strengthened the interaction with water with granulation time. The state of water in the MCC granules, which was controlled at the same level after drying, was believed to change with granulation time. The changes in the state of the water in the MCC granules were attributed to changes in the structure of the granules. That is, MCC formed a complicated network by becoming entangled after being divided by the shear force of the impeller during the wet granulation process. An X-ray diffraction study on the change of crystal state in MCC is described in another paper.⁹⁾

Kleinebudde reported that the wet MCC pellets prepared

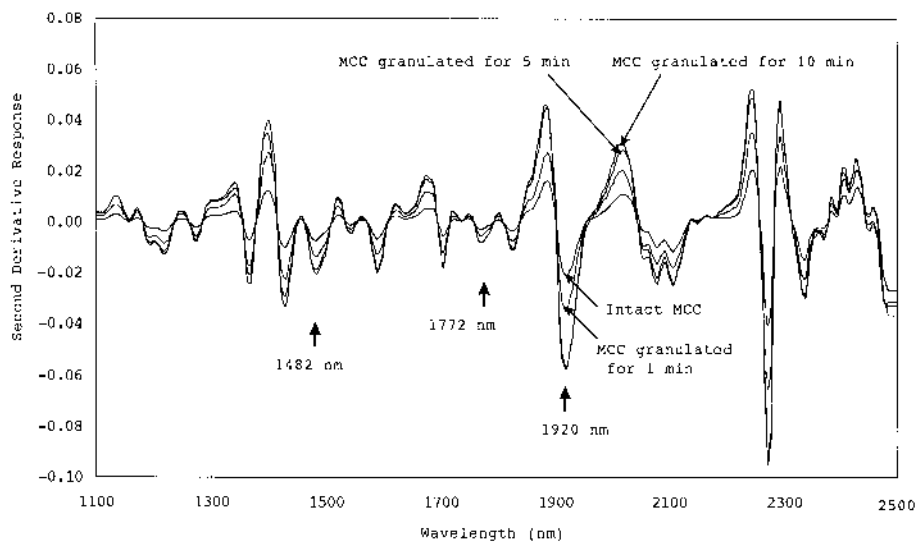


Fig. 5. The Second Derivatives of Spectra for Intact MCC and Dried MCC Granules

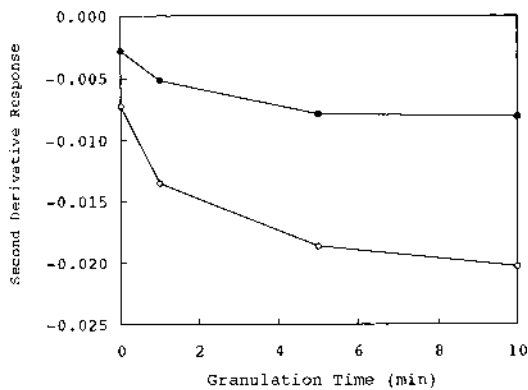


Fig. 6. Relationship between Granulation Time and Second Derivative Response of Near IR Spectra

○, 1482 nm, assignment: first overtone of O–H stretching vibration of cellulose molecule; ●, 1772 nm, assignment: first overtone of C–H stretching vibration of cellulose molecule.

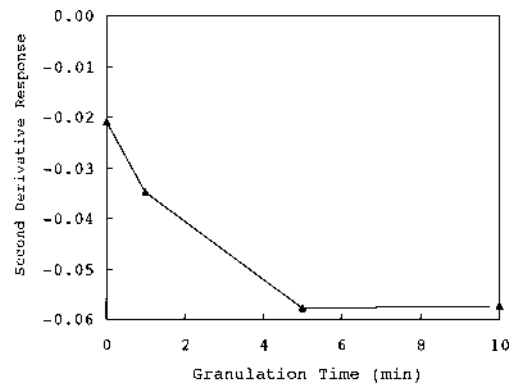


Fig. 7. Relationship between Granulation Time and Second Derivative Response of Near IR Spectra

▲, 1920 nm, assignment: the combination of O–H stretching and deformation vibration of water molecule.

by an extruder exhibited shrinking and densification properties by drying.¹⁷⁾ Therefore, MCC granules could retain water within their structure more tightly than intact MCC.

There are many reports in which the power consumption of the impeller was measured instead of shear force, because it is difficult to determine the shear force to powder mass directly during granulation.^{18–20)} Although power consumption is useful to determine the endpoint of granulation, it depends on the granulating conditions such as the quantity of water and powder loaded in a chamber, type of equipment, shape of impeller and so on. This means that power consumption does not, strictly speaking, express the shear force to powder mass. However it is important to estimate the strength of shear force to clarify the relationship between shear force and MCC behavior. Further study on development of an investigation method for shear force is required.

Zografi *et al.*¹²⁾ and Blair *et al.*²¹⁾ indicated that there were three stages of the adsorption process of water to MCC. There is an initial rapid sorption process as the first stage, at which stage water initially bonds as one molecule between two anhydroglucose units. The second stage is very slow, and involves a water molecule breaking the water/anhydroglucose bonds, and the formation of a one molecule to one anhydroglucose binding site stoichiometry. The third stage is more rapid movement towards equilibrium, in which adsorption of loosely bound water occurs. These three stages are not entirely separate, and there will be some overlap. A similar study was also performed by Buckton and Brezner.²²⁾ As the binding state of water to MCC could reflect the near IR spectra, we presumed that the dehydration rate could be different among the granules with different granulation time. Therefore, isothermogravimetric analyses of intact MCC and MCC granules were carried out.

The results of isothermogravimetric analysis are expressed as the weight change plotted against time (Fig. 8). The rate of dehydration at 30 °C decreased in the following order: intact MCC >> dried MCC granules granulated for 1 min > 5 min = 10 min. Initial slopes of the linear portion in isothermogravimetric analysis curves were calculated as the dehydration rate. The results were -0.789, -0.261, -0.211, and -0.208 for intact MCC, and MCCs granulated for 1, 5, and 10 min, respectively. These values were viewed to be the sum of dehydration rates for unchanged structure and changed structure in MCC. Therefore, the ratio of slopes for MCC granules to intact MCC was believed to be related to the ratio of changed parts in MCC (Fig. 9). Although these values will not express the ratio of changed parts in MCC quantitatively, these results can become an indicator for the change in structure of MCC granules. Figure 9 shows a similar tendency to near IR data (Fig. 6) as expected. Moreover, the observation that there was little difference in dehydration rate between dried MCC granules granulated for 5 and 10 min corresponded well with the near IR data. Therefore, it was the change in structure of MCC granules was expected to be completed within 5 min in this experiment. Our results confirmed that near IR spectrometry is useful to investigate the status of water in MCC. Fielden *et al.* carried out isothermogravimetric analysis for wet MCC pellets prepared using the extrusion method.⁶⁾ They reported that most water molecules were loosely bound to MCC, because 70 to 80% of absorbed water in MCC pellets exhibited dehydration behavior with

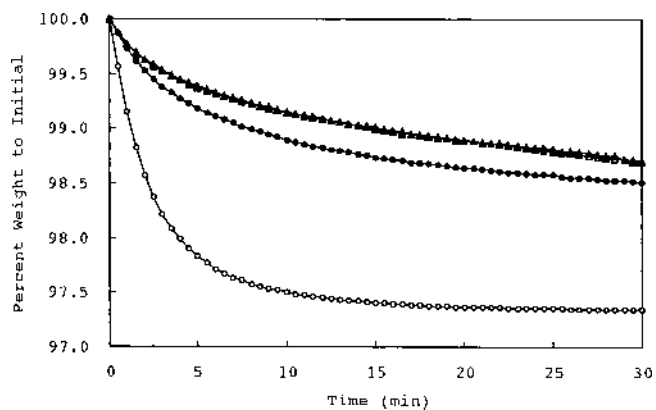


Fig. 8. Isothermogravimetric Analysis of Intact MCC and Dried MCC Granules at 30 °C

○, intact MCC; ●, MCC granulated for 1 min; △, MCC granulated for 5 min; ▲, MCC granulated for 10 min.

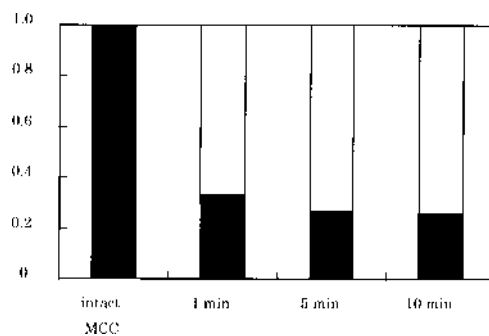


Fig. 9. Ratio of Slopes for MCC Granules in Isothermogravimetric Analysis Curves to Intact MCC

■, unchanged part in MCC; □, changed part in MCC.

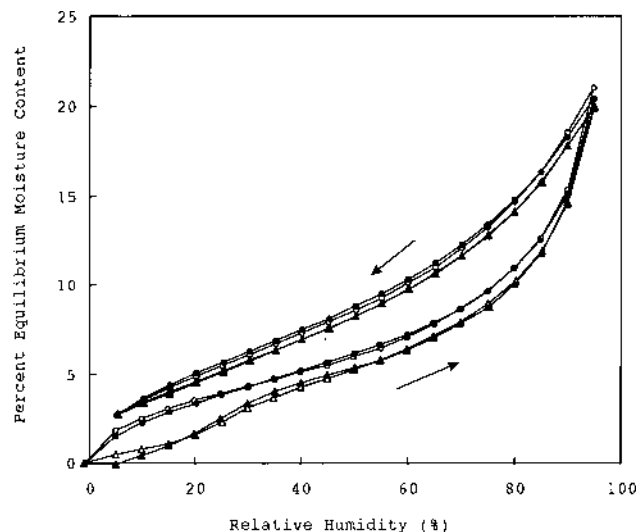


Fig. 10. Isothermal Adsorption Curves for Intact MCC and MCC Granules at 25 °C

○, intact MCC; ●, MCC granulated for 1 min; △, MCC granulated for 5 min; ▲, MCC granulated for 10 min.

zero-order kinetics. However, the water should bind with cellulose tightly in dried MCC granules, because granules including only 5 to 6% water were analyzed. Therefore, dehydration was depressed.

Water vapor adsorption isotherms for dried MCC granules and intact MCC are shown in Fig. 10. Dried MCC granules granulated for 1 min gave a sigmoid curve similar to intact MCC, while the dried MCC granules granulated for 5 and 10 min gave different curves from intact MCC. They showed lower adsorption characteristics in the range of about 5 to 40% relative humidity.

Zografi *et al.* reported that water adsorbed the amorphous region in MCC.¹² This amorphous region could have a looser structure than the crystalline region. Therefore, water would easily form hydrogen bonds with the amorphous region of intact MCC even under low humidity conditions. In contrast, MCC granules exhibited low adsorption behavior under conditions of low humidity. As isothermal adsorption data should reflect the difference in MCC structure, the main part changed in MCC granules was believed to be the amorphous region, that is, the ratio of the free hydroxyl groups in this amorphous region could be reduced by entanglement in shrunken MCC granules.

In the range of high relative humidity, all samples showed similar curves. As this range corresponds to the third stage described above, loosely bound water molecules, which interact little with MCC, were suggested to exist in MCC. Therefore, adsorption curves in the 80 to 90% range did not depend on the characteristics of MCC.

In the desorption process, all samples gave similar curves. Isothermogravimetric analysis indicated that the rate of dehydration of MCC granules decreased with granulation time due to formation of the network structure. However, no differences were observed in quantity of water among samples in desorption behavior, because the equilibrium state was reached in this experiment.

Conclusions

Near IR spectra data suggested that the degree of interaction between MCC and water gradually increased with granulation time. The results of isothermogravimetric analysis suggested that the structure of MCC changes during granulation to a structure that can hold water tightly. These results supported the reasoning that MCC would form a network due to entanglement of divided MCC particles. It was recognized

that near IR was useful to investigate the state of water in polymers.

In addition to these results, analyses of moisture adsorption isotherms suggested that these physical changes in MCC may occur primarily in the amorphous region.

References

- 1) Fielden K. E., Newton J. M., Rowe R. C., *Int. J. Pharm.*, **97**, 79—92 (1993).
- 2) Law M. F., Deasy P. B., McLaughlin J. P., Gabriel S., *J. Microencapsul.*, **14**, 713—723 (1997).
- 3) Kleinebudde P., Schröder M., Schultz P., Müller B. W., Waaler T., Nymo L., *Pharm. Dev. Technol.*, **4**, 397—404 (1999).
- 4) Habib Y. S., Abramowitz R., Jerzewski R. L., Jain N. B., Agharkar S. N., *Pharm. Dev. Technol.*, **4**, 431—437 (1999).
- 5) Tsukamoto T., Chen C. Y., Okamoto H., Danjo K., *Chem. Pharm. Bull.*, **48**, 769—773 (2000).
- 6) Fielden K. E., Newton J. M., O'Brien P., Rowe R. C., *J. Pharm. Pharmacol.*, **40**, 674—678 (1988).
- 7) Kleinebudde P., *Pharm. Res.*, **14**, 804—809 (1997).
- 8) Ek R., Newton J. M., *Pharm. Res.*, **15**, 509—510 (1998).
- 9) Suzuki T., Kikuchi H., Yamamura S., Terada K., Yamamoto K., *J. Pharm. Pharmacol.*, **53**, in press (2001).
- 10) Sacchetti M., *J. Pharm. Sci.*, **87**, 982—986 (1998).
- 11) Mayville F. C., Atassi F., Wigent R. J., Schwartz J. B., *Pharm. Dev. Technol.*, **4**, 467—474 (1999).
- 12) Zografi G., Kontny M. J., Yang A. Y. S., Brenner G. S., *Int. J. Pharm.*, **18**, 99—116 (1984).
- 13) Buckton G., Yonemochi E., Hammond J., Moffat A., *Int. J. Pharm.*, **168**, 231—241 (1998).
- 14) Buckton G., Yonemochi E., Yoon W. L., Moffat A. C., *Int. J. Pharm.*, **181**, 41—47 (1999).
- 15) Osborne B. G., Fearn T., Hindle P. H., "Practical NIR Spectroscopy with Application in Food and Beverage Analysis," Longman, Harlow, U.K., 1993, pp. 28—33.
- 16) Shenk J. S., Workmann J., Jr., Westerhaus M. O., "Application of NIR Spectroscopy to Agricultural Products," ed. by Burns D. A., Ciurczak E. W., Handbook of Near IR Analysis, Marcel Dekker, 1992, New York, pp. 393—395.
- 17) Kleinebudde P., *Int. J. Pharm.*, **109**, 209—219 (1994).
- 18) Leuenberger H., *Acta Pharm. Technol.*, **29**, 274—280 (1983).
- 19) Holm P., Schaefer T., Kristensen H. G., *Powder Technol.*, **43**, 225—233 (1985).
- 20) Ritala M., Holm P., Schaefer T., Kristensen H. G., *Drug Dev. Ind. Pharm.*, **14**, 1041—1060 (1988).
- 21) Blair T. C., Buckton G., Breezer A. E., Boomfield S. F., *Int. J. Pharm.*, **63**, 251—257 (1990).
- 22) Buckton G., Breezer A. E., *Int. J. Pharm.*, **41**, 139—145 (1988).