

Regular Article

The Solubility of Microcrystalline Cellulose in Sodium Hydroxide Solution Is Inconsistent with International Specifications

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Microcrystalline cellulose (MCC) is used globally as an inactive ingredient in food and nutraceutical products and is commonly used as a food additive. To confirm the conformity of MCC to the solubility requirements stipulated in international specifications, the solubilities of commercially available MCC products were tested in sodium hydroxide (NaOH) solution. All of the samples were insoluble in NaOH solution, which is inconsistent with the descriptions provided in international specifications. We also prepared celluloses with different degree of polymerization (DP) values by acid hydrolysis. Celluloses with lower DP were prepared using a three-step process, and their solubilities were tested in NaOH solution. These celluloses were found to be insoluble, which is inconsistent with the descriptions provided in international specifications. The present study suggests that the descriptions of the solubility of the celluloses in NaOH solution found in the current international specifications should be revised.

Key words microcrystalline cellulose; international specification; solubility; sodium hydroxide

Microcrystalline cellulose (MCC) is partially depolymerized cellulose prepared by treating alpha-cellulose obtained as pulp from fibrous plant materials with mineral acids, followed by purification. MCC is used globally as an inactive ingredient in food and nutraceutical products, and is a commonly used food additive that acts as a stabilizer, emulsifier, anti-caking agent, and dry-binder during food production. MCC is also used in oral pharmaceutical and cosmetics products. Consequently, the global volume of MCC production is increasing annually.

An article in Japan Petrochemical Newspaper (2010) estimated the global MCC sales volume to be 70000 tons per year. An article in Transparency Market Research (2015) reported that the global MCC market was worth US\$ 633 million in 2013 and was anticipated to grow at 5.8% CAGR (Compound Annual Growth Rate) from 2014 to 2020. Approximately 30% of the volume of MCC is used by the food and beverage industries, whereas the pharmaceutical industry uses about 40% of the global output. Based on the sales volume reported by Transparency Market Research (2015), and considering that the price of MCC has been US\$ 4–6 per kilogram, at least 70% of approximately 100000 tons

[\$633000000/\$6=105500 tons, or approximately 100000 tons] is consumed globally each year by the food, beverage and pharmaceutical industries.

Specifications for the use of MCC as a food additive have been established in the U.S. (Food Chemical Codex; FCC)¹⁾ and EU (E number: E No.)²⁾ and evaluated by the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA).³⁾ In addition, specifications for its use as a pharmaceutical excipient have been established in the U.S. Pharmacopeia/National Formulary (USP/NF)⁴⁾ and European Pharmacopoeia (Ph. Eur.).⁵⁾ The physicochemical properties of MCC used as a food additive and as a pharmaceutical excipient are essentially identical. The specifications establish the solubility of MCC in sodium hydroxide (NaOH) solution, but the descriptions of the solubility tests in the JECFA and EU specifications differ from those of other regulatory bodies (Table 1).

Since commercial MCC is used worldwide as a food additive, these discrepancies between the specifications could pose safety issues and cause trade disputes. Definitions of the solubility of a compound in a solvent as described in the JECFA compendium and according to the JECFA descriptive terms

Table 1. Description of the Solubility of MCC in NaOH Solution from Different Official Compendiums

Official compendium/Article	Description of solubility in sodium hydroxide solution
JECFA/Microcrystalline cellulose	Slightly soluble in sodium hydroxide solution
E Number/Microcrystalline cellulose	Slightly soluble in sodium hydroxide solution
FCC9th/Cellulose gel	Insoluble in dilute sodium hydroxide solutions
USP38/Microcrystalline cellulose	Practically insoluble in sodium hydroxide solution (1 in 20)
Ph. Eur. 8th/Cellulose, microcrystalline	Practically insoluble in a 50 g/L aqueous solution of sodium hydroxide

Microcrystalline cellulose and cellulose gel are synonyms.

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Table 2. Definitions of Solubility According to the JECFA

Descriptive term	Parts of solvent required for 1 part of solute			
Very soluble	Less than 1			
Freely soluble	From	1	to	Less than 10
Soluble	From	10	to	Less than 30
Sparingly soluble	From	30	to	Less than 100
Slightly soluble	From	100	to	Less than 1000
Very slightly soluble	From	1000	to	Less than 10000
Practically insoluble or insoluble	More than 10000			

are summarized in Table 2.

Solubility was visually evaluated to determine the solubility criteria stipulated in the various official compendiums listed in Table 1. In the JECFA description, the sample is completely dissolved if it falls into any category from “Very soluble” to “Very slightly soluble,” and is not completely dissolved if it falls into the “Practically insoluble or insoluble” category. “Very soluble” indicates that less than 1 part of solvent is required to solubilize 1 part of solute, and “Very slightly soluble” indicates that between 1000 to less than 10000 parts of solvent are required to completely dissolve 1 part of solute. However, “Practically insoluble or insoluble” indicates that even more than 10000 parts of solvent will not completely dissolve 1 part of solute and that a powder residue remains.

We therefore considered it important to investigate whether the solubility of commercial MCC in NaOH solution is consistent with the descriptions in the JECFA and EU specifications. The degree of polymerization (DP) of MCC might affect its solubility in NaOH solution, so we prepared celluloses with lower DP and tested their solubility. The solubilities of the celluloses in NaOH solution were found to be inconsistent with the descriptions in the JECFA and EU specifications.

MATERIALS AND METHODS

Samples Nine commercially available MCC products were used. Samples No. 1–3 are food additive grade and sample No. 4 is pharmaceutical excipient grade made by Asahi Kasei Corporation, and samples No. 5–9 are food additive grade purchased from American or German manufacturers. Samples No. 10 and 11 were prepared by us and samples No. 12 and 13 are commercial chemical reagents.

Reagents and Chemicals NaOH, sulfuric acid, and ammonia solution were purchased from Wako Pure Chemical Industries, Ltd., Osaka, Japan. DP was analyzed using cupri-ethylenediamine hydroxide solution purchased from GFS Chemicals, Inc., Columbus, OH, U.S.A. The NMR reagents acetone, lithium chloride (LiCl), and *N,N*-dimethylacetamide (DMAc) were purchased from Kishida Chemical Co., Ltd., Osaka, Japan, and dimethyl sulfoxide-*d*₆ (DMSO-*d*₆) was purchased from Cambridge Isotope Laboratories, Tewksbury, MA, U.S.A. Cellopentaose, sample No. 12, was purchased from Seikagaku Corporation, Tokyo, Japan. Cellobiose, sample No. 13, was purchased from Tokyo Chemical Industry Co., Ltd., Tokyo, Japan.

Preparation of NaOH Solution Various concentrations of NaOH solutions were prepared to investigate the effect on MCC solubility by dissolving NaOH (0.4–500 g) in deionized water (DW) to a total volume of 1000 mL.

Solubility Test in NaOH Solution Solubility in NaOH solution was determined as described in the JECFA compendium and according to the JECFA descriptive terms shown in Table 2. For example, 7–9 mg of each MCC sample was added to an Erlenmeyer flask containing 100 mL of NaOH solution (solute:solution=1:more than 10000), then the flask was placed on a rotatory shaker (150 rpm) for 5 min. The temperatures indicated in the Introduction to the JECFA compendium were used. The solubilities of MCC samples were evaluated visually. The presence of powder residue in the NaOH solution after adding MCC and shaking for 5 min was insoluble, therefore it was classified as “Practically insoluble or insoluble” in JECFA.

Analysis of DP The analysis was carried out in accordance with the method described in Identification 3 of MCC section in the Japanese Pharmacopoeia (JP) 16th edition. Briefly, the DP was calculated from the viscosity of the sample in cupri-ethylenediamine hydroxide solution. The sample (1.3 g) was completely dissolved in 25 mL of DW and 25 mL of 1 mol/L cupri-ethylenediamine hydroxide solution under a nitrogen atmosphere. The sample solution or a blank solution was poured into an Ubbelohde viscometer (Sibata Scientific Technology Ltd., Saitama, Japan) and the flow time was recorded. Each kinematic viscosity was calculated using the flow time and viscometer constant. The relative viscosity was calculated using the kinematic viscosity, and the intrinsic viscosity was determined by interpolation using Table 1 in MCC section. The DP was calculated using the following equation:

$$DP = [(95) \times [\eta]_c] / \{W_s \times [(100 - \%LOD) / 100]\}$$

$[\eta]_c$ = intrinsic viscosity

W_s = weight of MMC used (g)

%LOD = value obtained from the test for Loss on Drying
(1 g, 105°C, 3 h)

Preparation of Cellulose with Lower DP Sample No. 1 (25 g) was dispersed in 100 mL of 40 wt% sulfuric acid at 10°C, and then the concentration of sulfuric acid in the mixture was increased to 65 wt% by the addition of 72 wt% sulfuric acid at 20°C. The mixture was stirred slowly at 15°C until the MCC was completely dissolved, and then the dissolved MCC mixture was poured into 2673 mL of 10 wt% sulfuric acid or 3267 mL of DW to regenerate the cellulose (final concentration of sulfuric acid was 20 and 10 wt%, respectively). Each mixture with regenerated cellulose was then hydrolyzed by heating at 80°C for 30 min, and then the hydrolysate solution was poured into 15 L of DW to stop the reaction. After several hours, the clear supernatant was discarded and the pre-

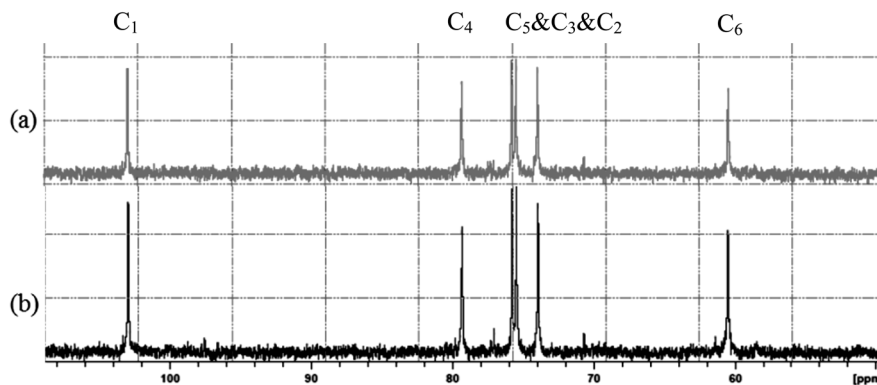
Table 3. Results of MCC Solubility of Sample No. 1 at Five NaOH Concentrations

NaOH concentration (g/L (mol/L))	Sample weight (mg)	Solvent quantity (mL)	Ratio Sample:Solvent	Result	Classification
500 (12.5)	967.4	100	1:103	Insoluble	“Very slightly soluble” or “Practically insoluble or insoluble”
	102.6	100	1:975	Insoluble	
320 (8)	962.4	100	1:104	Insoluble	“Very slightly soluble” or “Practically insoluble or insoluble”
	106.4	100	1:940	Insoluble	
160 (4)	102.6	100	1:975	Insoluble	“Very slightly soluble” or “Practically insoluble or insoluble”
20 (0.5)	103.3	100	1:968	Insoluble	“Very slightly soluble” or “Practically insoluble or insoluble”
0.4 (0.01)	107.0	100	1:935	Insoluble	“Very slightly soluble” or “Practically insoluble or insoluble”

Table 4. Results of MCC Solubility Tests in NaOH Solution

No.	Manufacturer	DP ^{b)}	Sample weight (mg)	Solvent quantity (mL)	Ratio Sample:Solvent	Result	Classification
1	Company A (Japan)	151	7.7	100	1:12987	Insoluble	“Practically insoluble or insoluble”
2		234	7.0	100	1:14286	Insoluble	“Practically insoluble or insoluble”
3		236	7.0	100	1:14286	Insoluble	“Practically insoluble or insoluble”
4 ^{a)}		234	8.0	100	1:12500	Insoluble	“Practically insoluble or insoluble”
5	Company B (U.S.A.)	237	7.9	100	1:12658	Insoluble	“Practically insoluble or insoluble”
6		240	7.9	100	1:12658	Insoluble	“Practically insoluble or insoluble”
7	Company C (Germany)	237	7.1	100	1:14085	Insoluble	“Practically insoluble or insoluble”
8		223	7.7	100	1:12987	Insoluble	“Practically insoluble or insoluble”
9		227	7.7	100	1:12987	Insoluble	“Practically insoluble or insoluble”

a) Pharmaceutical excipient-grade. b) DP was used with reference to Japanese Pharmacopoeia (JP). The concentration of NaOH solution was 50 g/L.

Fig. 1. ¹³C-NMR Spectra of Lower DP Cellulose (DP=76 (a) and DP=59 (b)) in Cellulose/LiCl/DMAc/DMSO-*d*₆=7/8/60/25 wt% Ratio

precipitate was washed with 10L of DW. This washing process was repeated more than 6 times until the ion conductivity of the wash water was below 100 μS/cm, at which point diluted ammonium solution was added to the final wash water to neutralize the pH. The cellulose was collected by suction filtration, dried at 60°C, then milled using an ultra-centrifugal mill (ZM200; Verder Scientific Co., Ltd., Tokyo, Japan) (aperture size 0.25 mm, speed 18000rpm) before use.

Confirmation of Chemical Structure Using NMR
¹³C-NMR was conducted to determine the chemical characteristics of the prepared lower DP cellulose powders. The solution for ¹³C-NMR measurements (cellulose/LiCl/DMAc/DMSO-*d*₆=7/8/60/25 wt% ratio) was prepared in a 5-mm tube. The cellulose sample was washed with acetone and DMAc, and then was dissolved in the LiCl/DMAc/DMSO-*d*₆ solution. Each sample solution was transferred to an NMR tube and ¹³C-NMR measurements were carried out at room temperature (AV-400M, Bruker, Billerica, MA, U.S.A.).

RESULTS AND DISCUSSION

Effects of Concentration of NaOH Solution The description for the solubility of MCC in NaOH solution in the JECFA specification is “Slightly soluble in NaOH solution.” The solubility of MCC in NaOH in the other specifications (FCC, USP/NF, and Ph. Eur.) is described as either “Insoluble” or “Practically insoluble.” The NaOH concentration described in USP/NF and Ph. Eur. is 50 g/L, whereas the NaOH concentration is not described in the JECFA. Therefore, we investigated the effects of NaOH concentration on the solubility of MCC.

As shown in Table 3, Sample No. 1, which has the lowest DP shown in Table 4 of the eight commercial food-additive-grade MCC products tested, was insoluble at all five NaOH concentrations in the solute: solvent range defined as “Slightly soluble.” Therefore, they were classified as “Very slightly soluble” or “Practically insoluble or insoluble” in JECFA. These

results show that the NaOH concentration does not affect the solubility of MCC in NaOH solution.

Investigation of the Solubility of Commercial MCC Products in NaOH Solution We investigated the solubility of nine commercially available MCC products in NaOH solution for the solute: solvent ratios defined as “Practically insoluble or insoluble,” and the results are shown in Table 4. A NaOH concentration of 50 g/L was used, in accordance with the condition described in Ph. Eur. All of the samples were insoluble, therefore they were classified as “Practically insoluble or insoluble” in JECFA. The result for sample No. 4, which was pharmaceutical excipient grade, was similar to those of samples No. 1–3 and No. 5–9, which were food additive grade, and indicates that the physicochemical properties of food additive and pharmaceutical excipient MCC products are identical.

Since the DP of MCC might affect solubility in NaOH, the DP of all the samples was measured and found to range from 150 to 240 (Table 4), in accordance with the JP specification. Several publications have reported the solubilization of cellulose in aqueous solutions of *N*-methyl morpholine-*N*-oxide (NMMO)⁶ and ionic liquids⁷ for the purpose of regenerating cellulose fibers and films, and the dissolution of cellulose

materials in NaOH solution has also been reported.⁸ A clear solution containing 2% dissolved cellulose in 5% NaOH solution was obtained in a dissolution test using Avicel (DP=190). However, dissolution could not be achieved using a simple method such as that described in the JECFA (*i.e.*, at room temperature and without preprocessing), but rather required swelling the cellulose in 7–13 wt% NaOH solution, followed by freezing, thawing, and then dilution.^{8,9} These reports support our results that commercial MCC products with DP=150–240 are not soluble in 5% NaOH solution without additional processing.

Solubility of Cellulose with Lower DP in NaOH Solution Isogai and Atalla reported that DP is a key factor for controlling the dissolution of cellulose in aqueous NaOH.⁸ The preparation of regenerated cellulose with different DPs (DP=23–179) was reported previously, and the influence of DP and crystallinity on the acid hydrolysis of cellulose was discussed.¹⁰ Low DP hindered the recrystallization of cellulose and improved its reactivity,¹⁰ but the solubilities of these celluloses in NaOH solution were not reported.

In the present study, celluloses with lower DPs (DP values of 59 or 76) were prepared using a three-step process. The

Table 5. Results of the Solubility Tests of Prepared Celluloses in NaOH Solution

No.	Sample type	DP ^{a)}	Sample weight (mg)	Solvent quantity (mL)	Ratio Sample:Solvent	Result	Classification
10	Prepared cellulose 1	59	8.6	100	1:11628	Insoluble	“Practically insoluble or insoluble”
11	Prepared cellulose 2	76	7.8	100	1:12820	Insoluble	“Practically insoluble or insoluble”
12	Cellopentaose	5	10.5	0.0945	1:9	Dissolved	“Freely soluble”
13	Cellobiose	2	100.1	0.9009	1:9	Dissolved	“Freely soluble”
			98.1	0.0883	1:0.9	Insoluble	

^{a)} Degree of polymerization was used with reference to Japanese Pharmacopoeia (JP). The concentration of NaOH solution was 50 g/L.

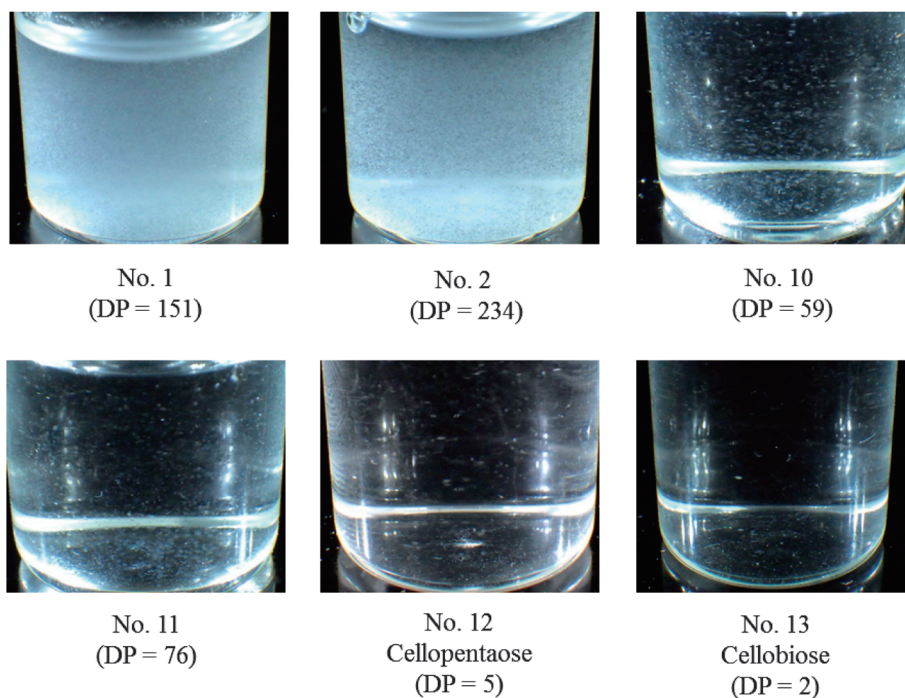


Fig. 2. Photographs of the Precipitate Remaining for MCC Products (Nos. 1 and 2) and Lower DP Celluloses (Nos. 10 and 11) Cellopentaose (No. 12) and Cellobiose (No. 13) are completely dissolved.

concentration of sulfuric acid used in the regeneration and hydrolysis steps regulates the DP of the regenerated celluloses.¹¹⁾ The samples were examined using ¹³C-NMR analysis. All observed signals were assigned to the six carbons of the repeating sugar subunits of normal cellulose, suggesting that no derivatization of the regenerated samples had occurred (Fig. 1).

The solubilities of sample No. 10 (DP=59) and No. 11 (DP=76) were investigated in the solute:solvent ratio defined as “Practically insoluble or insoluble.” Insoluble material remained in 5% NaOH solution, so they were classified as “Practically insoluble or insoluble” in JECFA (Table 5). The amount of insoluble MCC remaining after the solubility test is shown in Fig. 2 and the amount of remaining DP=59 appears to be less than that of DP=76.

Both cellopentaose and cellobiose completely dissolved in 5% NaOH solution in the solute:solvent ratio defined as “Practically insoluble or insoluble” (Fig. 2). They also completely dissolved under solute:solvent ratios defined as “Freely soluble,” although they were insoluble at solute:solvent ratios defined as “Very soluble” (Table 5). Therefore, they were classified as “Freely soluble” in JECFA. These results suggest that decreasing the cellulose DP increases the solubility of cellulose in NaOH solution, and that cellulose with a DP of less than 59 might dissolve in 5% NaOH solution. This is consistent with the report that hydrolytic efficiency is significantly improved when the DP is below 51.⁹⁾

Considerations for Food Additive Specifications for MCC Samples No. 10 (DP=59) and No. 11 (DP=76) were found to be insoluble, which were classified as “Practically insoluble or insoluble” in JECFA, although the amount of residue in the two samples was different. The results suggest that the solubilities of all the samples in NaOH solution are inconsistent with the JECFA and EU specifications, which list MCC as “Slightly soluble.” MCC manufactured in Japan have been sold as a food additive since 1978 and as a pharmaceutical excipient since 1970, and the physicochemical properties of these MCC are identical. The DP of commercial MCC samples used in this study ranged from 150 to 240, and we presume that the specifications for MCC in the JECFA and EU specifications were evaluated using similar commercial MCC (DP=150–240).

The JECFA specification is very important in international commerce and this discrepancy in the solubility of MCC in NaOH solution might lead to trade disputes. Therefore, a revision of the description of the solubility of MCC in NaOH solution in the current JECFA specification is required for the international trade of commercial MCC.

CONCLUSION

We investigated the solubilities of nine commercial MCC products in NaOH solution and the results for all the samples were inconsistent with the description in the JECFA specification. We also investigated the solubility of a commercial MCC

(sample No. 1) at several NaOH concentrations. The NaOH concentration does not affect the solubility of MCC in NaOH solution. We further examined the solubility of two prepared celluloses with lower DP and found that the solubilities of these samples were also inconsistent with the description in the JECFA specification. Taking all these results into consideration, we would like to suggest a revision of the description for the solubility of MCC in NaOH solution in the current JECFA specification.

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Conflict of Interest Ichiro Kamei, Kyoko Sato and Hiroshi Akiyama have no conflict of interest. Hanayo Kodama and Yoshinaga Tamura are employees of the Asahi Kasei Corporation, Chiyoda-ku, Tokyo, Japan.

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