Effect of Hydrophobically-Modified Hydroxypropyl Methylcellulose on the Crystallization from Supersaturated Solutions of Indomethacin[1)]

Kaori IKEDA,*,[a] Izumi SAITOH,[a] Takayoshi OGUMA,[b] and Yasushi TAKAGISHI[b]

Developmental Research Laboratories, Shionogi & Co., Ltd.,[a] 2–1–3, Kuise Terajima, Amagasaki, Hyogo 660, Japan and Developmental Research Laboratories, Shionogi & Co., Ltd.,[b] 5–12–4, Sagisu, Fukushima-ku, Osaka 553, Japan.

Received April 13, 1994; accepted July 14, 1994

Hydrophobically-modified hydroxypropyl methylcellulose (HM-HPMC), possessing long-chain alkyl groups, is a new thickening agent for gel preparations. The solubility of indomethacin (IM) in supersaturated solutions increased with HM-HPMC concentration, but HM-HPMC did not solubilize IM crystals. This is not due to the suppression of the transformation of IM crystals from α to γ. HM-HPMC would thus appear to suppress the crystallization of IM from supersaturated solutions. Nucleation and crystal growth rates in a supersaturated solution of IM in the absence and presence of HM-HPMC were determined by measuring light transmittance under cooling. It became clear that HM-HPMC caused a slight stimulation of nucleation and a strong suppression of crystal growth. This activity of HM-HPMC was derived from the original polymer, HPMC, but was greater than that of HPMC itself. The suppression of crystal growth by HM-HPMC may thus be due to the hydrophobic interaction between hydrophobic regions, particularly long-chain alkyl groups, and IM molecules.

Keywords hydrophobically-modified; hydroxypropyl methylcellulose; crystal growth; nucleation; indomethacin; long-chain alkyl group

Hydrophobically-modified hydroxypropyl methylcellulose (HM-HPMC) is a polymer having long-chain alkyl groups in place of some of the hydroxyl groups of hydroxypropyl methylcellulose (HPMC), a water soluble cellulose derivative. The substitution of hydroxyl groups with alkyl groups was conducted to bring about hydrophobic interactions, and thus increase viscosity.[2a)] To use HM-HPMC as an ingredient of gel bases, this polymer was studied and found to have the following advantages[2a,b)]: 1) Solutions of HM-HPMC are highly viscous and show plasticity. 2) The viscosity of a solution of HM-HPMC is stable and independent of pH. 3) Gel preparations can be made easily with HM-HPMC. 4) HM-HPMC does not affect the stability of drugs present in gel preparations. 5) Drug release *in vitro* and percutaneous absorption *in vivo* from a gel preparation with HM-HPMC is the same as from conventional gel preparations.

This polymer may be able to solubilize drugs of low water-solubility.[2b)] The use of HM-HPMC in gel preparations increases the solubility of poorly-soluble drugs. Gel preparations can thus be obtained with drugs that precipitate in conventional carboxyvinyl polymer gel preparations. This feature prompted an examination of the effects of HM-HPMC on the solubility of indomethacin (IM) as a model drug to clarify the mechanism involved in the increase in solubility.

Experimental

Materials HM-HPMC and HPMC were HM- 90SH100000 of three different grades containing 0.6, 1.2, and 1.8% of long-chain alkyl groups and 90SH100000, respectively, and were obtained from Shin-Etsu Chemical Co., Ltd. (Niigata, Japan). IM was purchased from Sigma (U.S.A.), and methanol and isopropanol from Kanto Kagaku (Tokyo, Japan). All solvents and reagents, including the above reagents, were of special grade.

IM Concentration Determination About an 800 μl portion of a test solution was accurately weighed. Parahydroxybenzoic acid *n*-butyl ester dissolved in methanol was added as the internal standard. This mixture was diluted with methanol and analyzed by HPLC. The HPLC system (Waters, U.S.A.) was comprised of a Model 486 variable-wavelength UV detector, model 600E high pressure pump, model 717 autosampler, and a Novapak C_{18} column, 4 mm i.d. × 15 cm. The detection wavelength was set at 254 nm. The mobile phase was a 52 : 48 mixture of aqueous RCSS reagent (Waters, U.S.A.) and acetonitrile. The flow rate was 1 ml/min.

Measurement of Polymer Solution Viscosity a) HM-HPMC containing 1.8% of long-chain alkyl groups and HPMC were dissolved in a mixture of 0.02 M phosphate buffer solution (pH 4.0)–isopropanol–methanol (3 : 1 : 0.674, w/w/w) between 0.005% and 0.02%. Solution and solvent viscosities were measured at room temperature with a cone-plate type rotational viscometer (Tokyo Keiki, Tokyo, Japan). b) HM-HPMC containing 0.6% long-chain alkyl groups was dissolved in 0.02 M phosphate buffer solution (pH 4.0) at 0.05% to 0.6%. To 50 g of the solution was added 10 ml of methanol. The mixture was shaken for 1 h and viscosity was measured at room temperature with a Brookfield rotational viscometer (Tokyo Keiki, Tokyo, Japan). Solutions of HPMC were prepared similarly and viscosity was measured.

Enhancer Effects of HM-HPMC on Solubility a) About 800 mg of crystals of IM were dissolved in 50 ml of methanol. The solution was left in a cold place (4 °C) for recrystallization. The crystals thus obtained were dried at 40 °C for 1 h on a round No. 6 filter paper, 3 cm in diameter (Toyo Roshi, Tokyo, Japan) and ground in an agate mortar with a pestle. X-Ray diffraction patterns were observed for the original crystals before recrystallization (type 1) and recrystallized crystals (type 2) using a RINT 1100 X-ray diffractometer (Rigaku Denki, Tokyo, Japan) at a scanning speed of 2°/min at an angle 2θ from 2° to 40°. b) HM-HPMC containing 1.8% of long-chain alkyl groups and HPMC were dissolved in a mixture of 0.02 M phosphate buffer solution (pH 4.0)–isopropanol–methanol (3 : 1 : 0.674, w/w/w) at 0.005% to 0.02%. About 30 mg of type 1 crystals were added to 30 ml of each polymer solution and solvent. The mixture was shaken at room temperature for 3 d. After centrifugation at 20000 rpm for 10 min with a model J2-MC centrifuge (Beckman, U.S.A.), the concentration of IM in the supernate was determined. c) In a mixture of 0.02 M phosphate buffer solution (pH 4.0)–isopropanol–methanol (3 : 1 : 0.632, w/w/w), 0.2% solutions of HM-HPMC of the three different grades and HPMC were prepared. To about 6 ml of each polymer solution or solvent were added 10 mg of type 1 or type 2 IM crystals. The mixture was shaken at room temperature for 3 d. After centrifugation at 20000 rpm for 10 min, the concentration of IM in the supernate was determined.

Stabilization of Supersaturated IM Solution with HM-HPMC a) In a mixture of 0.02 M phosphate buffer solution (pH 4.0)–isopropanol (3 : 1, w/w), 0.005—0.02% solutions of HM-HPMC of three different grades and HPMC were prepared. To 15 ml of each solution and solvent were added 3 ml of methanol containing 20 mg of IM per ml. The mixture was shaken for 1 h to obtain a supersaturated IM solution, which was then left at room temperature for 7 d. The solution was centrifuged at 20000 rpm for 10 min and IM concentration in the supernate was determined. b) In 0.02 M phosphate buffer (pH 4.0), 0.05—0.6% solutions of HM-HPMC containing 0.6% of long-chain alkyl groups and HPMC were prepared. To 5 g of each solution and solvent alone was added 1 ml of methanol containing 20 mg of IM per ml. The mixture was shaken for 1 h. The supersaturated solution obtained was left at room temperature for 1 d. After centrifugation at 20000 rpm for 10 min, the IM concentration in the supernate was determined.

Observation of Crystals of IM Deposited from Supersaturated Solutions a) Crystals of IM deposited from a supersaturated solution were separated on No. 6 filter paper, 3 cm in diameter, dried at 40 °C for 1 h, and examined under a polarization microscope (Nikon, Tokyo, Japan). b) Crystals of IM obtained in the experiment a) and reagent crystals were compared by X-ray diffraction and differential scanning calorimetry (DSC). A model DSC 200 (Seiko Instruments Inc., Tokyo, Japan) was used for the latter measurement by linear heating at 10 °C/min from 60 °C to 200 °C.

Effects of Crystal Seeding into the Supersaturated Solution Type 2 crystals, recrystallized in the experiment above, were used as seeds. In a mixture of 0.02 M phosphate buffer solution (pH 4.0)–isopropanol (3 : 1, w/w), 0.2% solutions of HM-HPMC containing 1.8% of long-chain alkyl groups and HPMC were prepared. To 12.5 g of each solution and solvent were added 2.5 ml of methanol containing 5 mg of IM per ml. The mixture was shaken for 1 h. Duplicate supersaturated solutions were prepared in the same manner. To some of these solutions were added 8 mg of crystals as seeds, and the concentration of IM was monitored in either case.

Patterns of Crystal Precipitation from Supersaturated IM Solutions a) Measurement of the saturation temperature of solutions with various concentrations of IM: 5 g of a mixture of 0.02 M phosphate buffer solution (pH 4.0)–isopropanol (3 : 1, w/w) were placed in a glass stoppered test tube. To the test tube was added 1 ml of methanol containing IM at various concentrations. The system was mixed to obtain a test solution whose concentration was C_s. The test tube was cooled in a cold water bath (10 °C) until crystals were deposited, and shaken in a Personal-11 thermostat (Taitec, Saitama, Japan) to raise the temperature gradually at about 1 °C/min. When all crystals had disappeared, the temperature, θ_s, as the saturation temperature at C_s was recorded. b) Nucleation and crystal growth: HM-HPMC containing 1.8% of long-chain alkyl groups and HPMC were dissolved in a mixture of 0.02 M phosphate buffer solution (pH 4.0)–isopropanol (3 : 1, w/w) to obtain 0.2% solutions. A 2.5 g portion of each solution and solvent was weighed and placed in a quartz stoppered cell, then heated to and maintained at 65 °C. To the quartz cell was added 0.5 ml of methanol containing a variable amount of IM. The mixture was thoroughly mixed in the quartz cell, and the concentration of IM was taken as C_s. The water-jacketed cell holder of a model DU7500 spectrophotometer (Beckman, U.S.A.) was connected to a type T water bath (Haake, Germany) temperature controlled with a type N2 temperature controlling unit (Haake, Germany) in conjunction with a PG10 programming device (Haake, Germany). The water was circulated between the bath and cell-holder. The cell-holder was thus kept at a temperature 3—10 °C higher than θ_s, the saturation temperature of the test solution. A quartz stoppered cell containing a test solution of appropriate concentration was placed in the cell-holder and left for 5 min for equilibration. The temperature was lowered at a constant rate (b, °C/min) to 0 °C. Transmittance ($\lambda = 500$ nm) of the test solution was measured at intervals of 30 s during solution cooling.

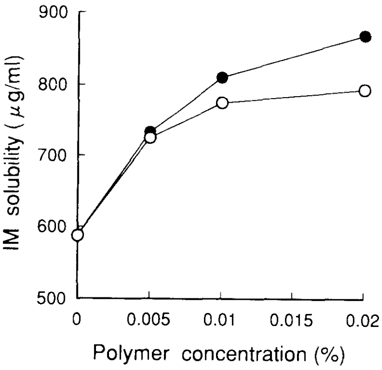

Fig. 1. IM Solubility in Supersaturated Solutions as a Function of Polymer Concentration

● , HM-HPMC; ○ , HPMC. Solvent composition: 0.02 M phosphate buffer solution (pH 4.0) : isopropanol : methanol = 3 : 1 : 0.674 (w : w : w). HM-HPMC; alkyl group content 1.8%.

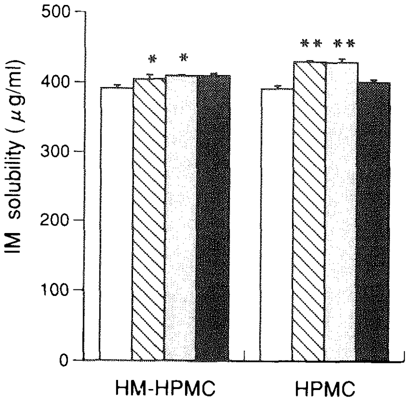

Fig. 2. Influence of Polymers on IM Solubility

Polymer concentration; □, 0%; ▨, 0.005%; □, 0.010%; ■, 0.020%. Each value is the mean + S.D., $n=3$. Significantly different from solvent (polymer concentration 0% solution) with $*p<0.01$, $**p<0.001$. Solvent composition: 0.02 M phosphate buffer solution (pH 4.0) : isopropanol : methanol = 3 : 1 : 0.674 (w : w : w). HM-HPMC; alkyl group content 1.8%.

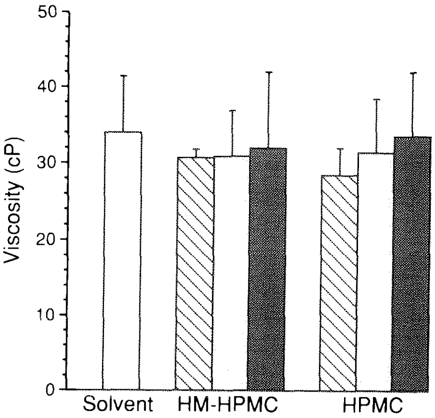

Fig. 3. Viscosity of Solutions

Polymer concentration; □, 0%; ▨, 0.005%; □, 0.010%; ■, 0.020%. Each value is the mean + S.D., $n=3$. Solvent composition: 0.02 M phosphate buffer solution (pH 4.0) : isopropanol : methanol = 3 : 1 : 0.674 (w : w : w). HM-HPMC; alkyl group content 1.8%.

Results and Discussion

Ability of HM-HPMC to Enhance Solubility and Stabilize Supersaturated Solutions When a portion of the highly concentrated IM solution in methanol was added to a polymer solution and solvent, the solutions became supersaturated. In these solutions, crystallization occurred and the solubility of IM decreased with time. However, the solubility of IM eventually became stable, and was measured. The solubility of IM in polymer solutions of very low concentration (0.005—0.02%) was maintained at a much higher supersaturated level than that in the same solvent but with no polymer (Fig. 1). Solubility increased with the concentration of the polymer. In addition, the solubility in the solution containing HM-HPMC was higher than in the solution containing HPMC. When crystals of IM were dissolved directly in the same polymer solutions as above, solubility in the solutions of either polymer was slightly higher than in the solvent containing neither polymer (Fig. 2). The slightly higher solubility indicates that these polymers may have the ability to enhance the solubility of IM, but such an increase was not significant as Fig. 1 shows. HM-HPMC or HPMC may not solubilize IM crystals, but may stabilize supersaturated solutions of IM due to their suppression of crystal precipitation. This stabilizing activity of HM-HPMC was derived from the original polymer, HPMC, but was greater than that of HPMC itself. The pattern of molecular diffusion of a solute or the viscosity of a solution are the most important factors affecting crystal growth leading to crystal precipitation. Solutions of HM-HPMC or HPMC at very low concentrations (0.005—0.02%) had essentially the same viscosity as the solvent itself (Fig. 3). However, the deposition of crystals was suppressed in the polymer solutions, indicating that the suppression of crystal deposition due to these polymers was apparently not the result of the suppression of IM molecular diffusion.

IM can exist in three different crystal forms, α, β and γ,[3] with crystals of the α form possessing higher solubility than the γ form.[4] When recrystallized, according to Ostwald's law, crystals of the α form are first deposited, then converted to the γ form gradually.[5] Solubility values in Fig. 1, which are higher than any value in Fig. 2, may be measured as the solubility of the α form, and hence, the transformation from α to γ may be responsible for the higher solubility in the presence of HM-HPMC or HPMC than in its absence. To confirm this possibility, we measured the solubility of the crystals of both forms in the presence of HM-HPMC and HPMC. It was confirmed by the X-ray diffraction pattern in advance that types 1 and 2 crystals had the γ and α forms, respectively, although type 2 crystals contained some crystals of the γ form. To measure the solubility of different crystal forms, these two types of crystals were dissolved directly in solutions containing HM-HPMC and HPMC. The solubility of the α form was much higher in the presence of the polymer than in its absence, whereas with crystals of the γ form, solubility was only somewhat higher than in the solvent containing neither polymer: the solubilities were essentially the same (Fig. 4). When measured in the absence of a polymer, the solubility of the α form was similar to that of the γ form, possibly due to the prompt transformation of the crystals from α to γ in the solvent not containing a polymer. The solubility of the γ form thus had to be measured in both instances. This suggests that HM-HPMC and HPMC may suppress the transformation of crystals from α to γ, or suppress the precipitation of crystals of the α form. As Fig. 1 shows, the solubility of IM measured in polymer solutions of very low concentrations (0.005—0.02%) is much higher than the solubility of the α form in 0.2% polymer solutions, indicating that these polymers possibly have a strong ability to suppress the precipitation of crystals of the α form before transformation from α to γ. The activity of these polymers, which increase the solubility of IM, may thus be the main factor for the suppression of precipitation in a supersaturated solution.

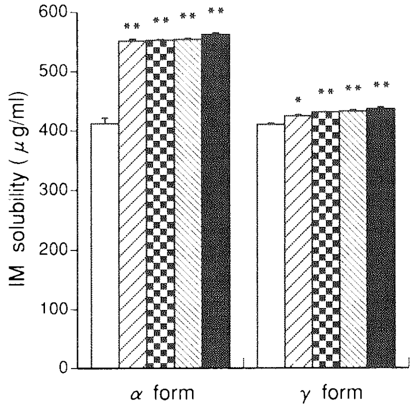

Fig. 4. Influence of Polymers on Solubility of IM Polymorphs (α and γ Form)

□, solvent; ▩, HM-HPMC (0.6); ▧, HM-HPMC (1.2); ■, HM-HPMC (1.8); ▨, HPMC (0); Values in parentheses are alkyl group content %. Each value is the mean + S.D., $n=3$. Significantly different from solvent with $^{*}p<0.01$, $^{**}p<0.001$. Polymer concentration: 0.2%. Solvent composition: 0.02 M phosphate buffer solution (pH 4.0) : isopropanol : methanol = 3 : 1 : 0.632 (w : w : w).

Crystals of IM Deposited from Supersaturated Solutions Crystals of IM deposited from supersaturated solutions were observed under polarization microscopy. Crystals deposited from the solvent containing neither polymer produced large needle-shaped crystals (Fig. 5b). In contrast, crystals deposited from the solution containing either HM-HPMC or HPMC were fine, spherical aggregates (Fig. 5c, d). X-Ray diffraction patterns showed all products of recrystallization to have the α form, with or without a polymer in solution, and reagent crystals to have the γ form (Fig. 6). The measurement of DSC indicated that reagent crystals had a melting point of the γ form, whereas crystals separated from supersaturated solutions had that of the α form (Fig. 7). These results support that the higher solubility in the presence *vs.* absence of a polymer is due not to the suppression of transformation of IM crystals from α to γ, but to the suppression of α form crystal precipitation. The recrystallization of IM by a titration technique from an aqueous solution of IM containing β-cyclodextrin has been shown to give rise to crystals of a form different from the three known forms.[6] Unlike β-cyclodextrin, neither HM-HPMC nor HPMC was able to produce crystals of an unusual form, nor was there any indication that IM and polymer form a complex or are coprecipitated. The difference in the appearance of crystals deposited from solutions of different solution systems, as observed with a polarization microscope, may be due to the suppression of crystal growth owing to the presence of a polymer.

Effects of Crystal Seeding into the Supersaturated Solutions When a solution of low concentration of IM in methanol was added to polymer solutions and solvent, supersaturated solutions remained supersaturated even 240 h later, regardless of the presence or absence of a polymer (Fig. 8a), since the supersaturated solubility of IM was low and, consequently, the crystallization of IM was very slow, even in the solvent. However, crystallization was accelerated by the addition of IM crystals as seeds to the solutions, leading to a decreased concentration of IM dissolved with time, which was much slower in the presence of HM-HPMC or HPMC than in its absence (Fig. 8b). These polymers may thus suppress crystal growth.

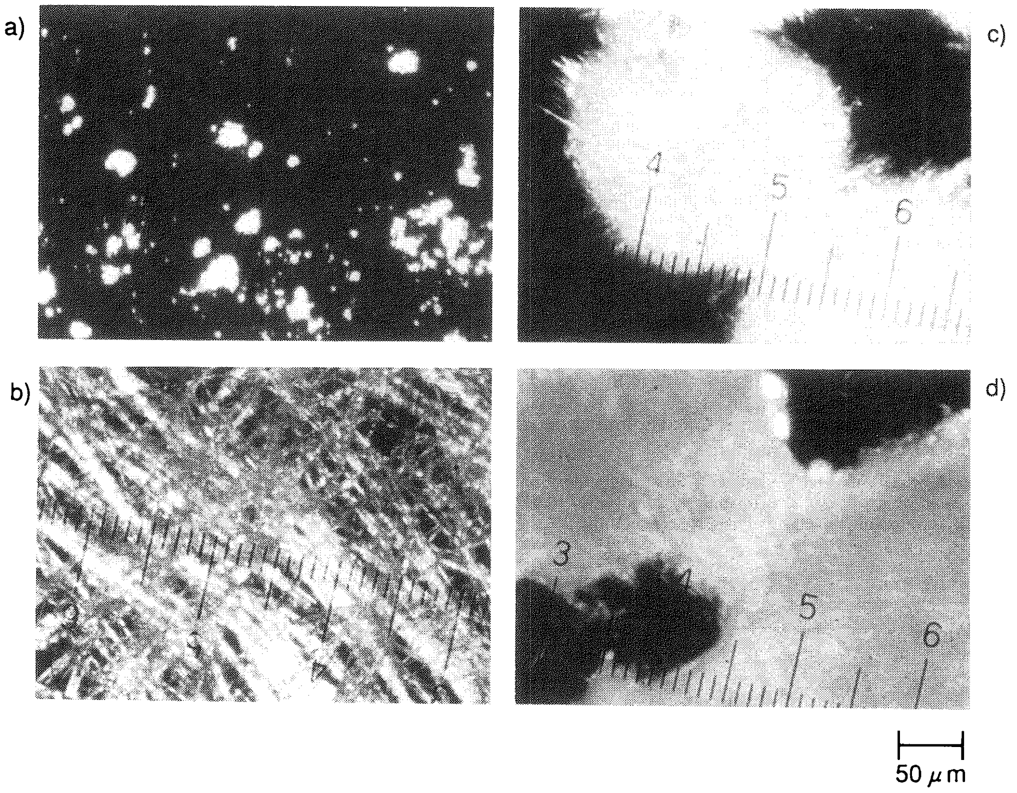

Fig. 5. Microphotographs of a) Reagent Crystals, and Precipitated Crystals from b) Solvent c) HM-HPMC Solution d) HPMC Solution

Solvent composition: 0.02 M phosphate buffer solution (pH 4.0) : isopropanol : methanol = 3 : 1 : 0.674 (w : w : w). HM-HPMC; alkyl group content 1.8%. Polymer concentration : 0.02%.

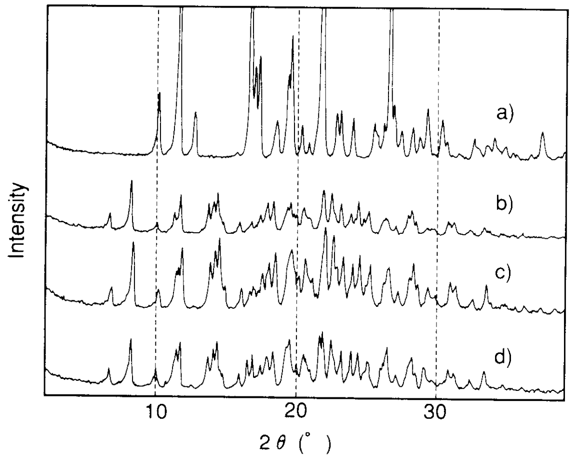

Fig. 6. X-Ray Diffraction Spectra of a) Reagent Crystals and Precipitated Crystals from b) Solvent c) HM-HPMC Solution d) HPMC Solution

Solvent composition: 0.02 M phosphate buffer solution (pH 4.0) : isopropanol : methanol = 3 : 1 : 0.674 (w : w : w). HM-HPMC; alkyl group content 1.8%. Polymer concentration: 0.02%.

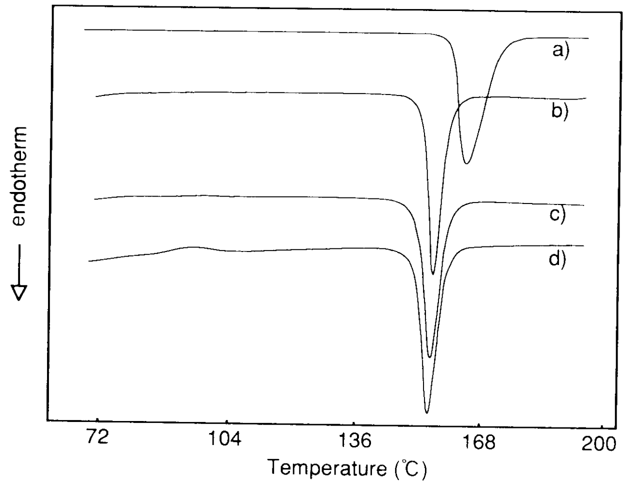

Fig. 7. DSC Profiles of a) Reagent Crystals, and Precipitated Crystals from b) Solvent c) HM-HPMC Solution d) HPMC Solution

Solvent composition: 0.02 M phosphate buffer solution (pH 4.0) : isopropanol : methanol = 3 : 1 : 0.674 (w : w : w). HM-HPMC; alkyl group content 1.8%. Polymer concentration: 0.02%.

Effects of HM-HPMC on Nucleation and Crystal Growth Rates The process of deposition of a solute from a supersaturated solution depends on two factors: nucleation rate and subsequent crystal growth rate. Hasegawa *et al.* report that polymers of the cellulose group suppress the precipitation of nifedipine crystals through the suppression of growth.[7] They did not study the effects on nucleation. No precise study has been done on the process of nucleation. Leeden *et al.* have recently made a kinetic study of this process.[8] In the present study, light transmittance reduced when crystals are formed in supersaturated solutions was used to measure nucleation and crystal growth rates. For the former, induction time is usually measured. However, because HM-HPMC strongly suppressed the deposition of crystals, when supersaturated solutions whose supersaturated solubility

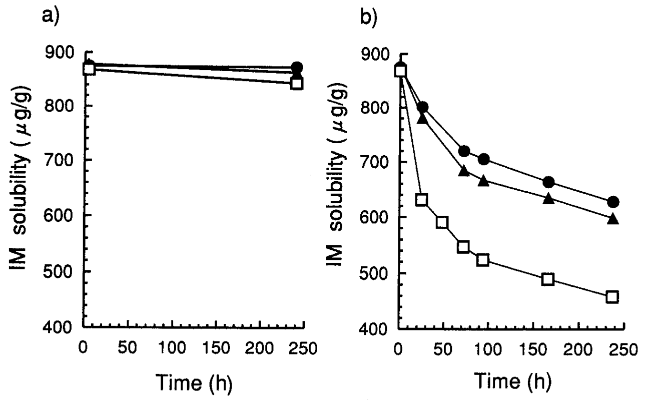

Fig. 8. Time Course of IM Solubility in Supersaturated Solutions under a) Unseeded Condition, and b) Seeded Condition.

—●—, HM-HPMC; —▲—, HPMC; —□—, solvent. Solvent composition: 0.02 M phosphate buffer solution (pH 4.0) : isopropanol : methanol = 3 : 1 : 0.632 (w : w : w). HM-HPMC; alkyl group content 1.8%. Polymer concentration: 0.2%.

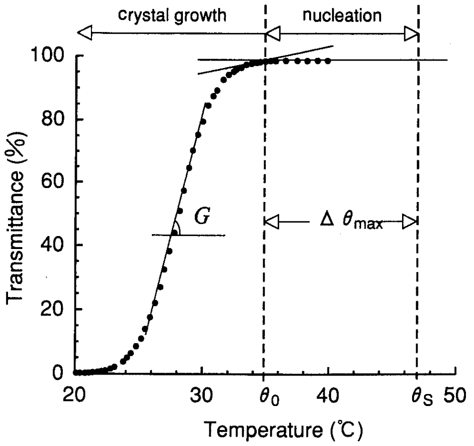

Fig. 9. Schema of Studying the Crystallization by Measuring the Light Transmittance

of IM was low were left for a long time at a constant temperature, hardly any crystals were deposited, making it difficult to measure induction time. The method of Mullin *et al.*[9] was thus used as an alternative. Supersaturated solutions were cooled at a constant rate to induce crystallization, and the value corresponding to the induction time was measured to calculate the nucleation rate. Figure 9 shows the transmittance *vs.* temperature curve obtained by cooling a test solution of IM at a constant rate (b) with a spectrophotometer equipped with a jacketed cell holder at a wavelength of $\lambda = 500$ nm, where IM has no absorbance. The solution remained supersaturated from θ_s to θ_0. The nucleation rate (J) is given as Eq. 1.[9]

$$J = (\Delta C_{\max} / \Delta \theta_{\max}) \cdot b \tag{1}$$

where $\Delta\theta_{\max} = \theta_s - \theta_0$, $\Delta C_{\max} = C_s - C_0$, θ_s: saturation temperature at the concentration of C_s (°C), θ_0: temperature of nucleation (°C), C_s: concentration of IM in the test solution (μg/g), C_0: concentration of IM in saturated solution at θ_0 (μg/g).

The temperature measured when the transmittance began to decrease was taken as θ_0, and J was calculated from Eq. 1. Too low or too high θ_0 is difficult to measure, and thus C_s was set between 3453 and 6047 μg/g. Crystal growth rate (G) was defined as the maximum rate of decrease in transmittance after θ_0.

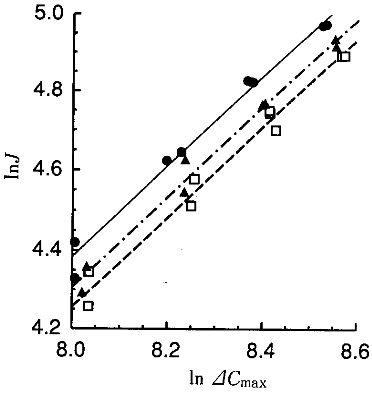

Fig. 10. Influence of Polymers on Nucleation Rate (J)

--□--, solvent; —●—, HM-HPMC, —·—▲—·— HPMC. Solvent composition: 0.02 M phosphate buffer solution (pH 4.0) : isopropanol : methanol = 3 : 1 : 0.632 (w : w : w). HM-HPMC; alkyl group content 0.6%. Polymer concentration: 0.2%.

Table I. Estimated Value of Slope (m; Nucleation Order) and Intercept ($\ln K_n$, K_n; Nucleation Rate Constant)

	Solvent	HM-HPMC	HPMC
m	1.13	1.13	1.13
$\ln K_n$	−4.817	−4.688	−4.766
K_n ($\times 10^{-3}$)	8.09	9.21	8.51

Table II. Difference in Estimated Intercept ($\ln K_n$)

Comparison pair	Difference in $\ln K_n$	99% confidence interval
Solvent : HM-HPMC	−0.129	−0.169— −0.090
Solvent : HPMC	−0.052	−0.091— −0.012
HM-HPMC : HPMC	0.078	0.038— 0.117

According to Nývlt,[10] the nucleation rate (J) is given as,

$$J = K_n \cdot \Delta C_{\max}^m \tag{2}$$

The logarithm of Eq. 2 gives,

$$\ln J = \ln K_n + m \cdot \ln \Delta C_{\max}. \tag{3}$$

Equation 3 indicates that there is a linear relationship between $\ln J$ and $\ln \Delta C_{\max}$. The slope (m) of the line of this equation represents the order of reaction kinetics of nucleation, and K_n calculated from the intercept ($\ln K_n$) of the line is the rate constant for nucleation. When $\ln J$, calculated with measured J, was plotted against $\ln \Delta C_{\max}$, the lines were satisfactorily linear regardless of the presence or absence of HM-HPMC or HPMC (Fig. 10). Regression analysis showed there was no statistically significant difference in the slope (m) among these lines. The slope of the lines was estimated as $m = 1.13$ (Table I). Thus, the presence of either polymer does not affect the order of reaction kinetics of nucleation. With estimates of the intercept (Table I), regression analysis showed a significant difference between any pair of values of the rate constant for nucleation, because zero was not included in any 99% confidence interval (Table II). The order of the rate constant for nucleation was HM-HPMC > HPMC > solvent. HM-HPMC and HPMC can thus accelerate nucleation, albeit slightly.

Table III shows the maximum rate of decrease in transmittance which represents the crystal growth rate (*G*). *G* for the solvent not containing a polymer was largest, regardless of IM concentration in the test solution. Values measured in the presence of HPMC and HM-HPMC were about half and 14%, respectively, of that measured in the solvent containing neither polymer. Thus, these two polymers, particularly HM-HPMC, suppress crystal growth.

The above findings suggest that HM-HPMC and HPMC, particularly HM-HPMC, have the strong ability to suppress the growth of core crystals, with the consequent effective suppression of crystal precipitation in supersaturated solutions, despite activity to accelerate nucleation preceding growth. Uekama *et al.* state that the crystal growth of nifedipine is suppressed in amorphous dispersions produced by spray-drying it with 2-hydroxypropyl-β-cyclodextrin (HP-β-CyD) because nifedipine molecules are incorporated into hydrophobic clefts of the HP-β-CyD molecule, thus being prevented from binding to each other. Hence, crystal structure of a higher order is not possible.[11] We noted a similar situation in HM-HPMC solutions. IM molecules enter hydrophobic regions formed by the intermolecular hydrophobic association of HM-HPMC by the action of long-chain alkyl groups, leading to localized high concentrations of IM, which accelerates initial crystallization to form core crystals. IM molecular attachment to the surface of core crystals to form a crystal structure is interfered with because IM molecules are trapped in hydrophobic interactions with the hydrophobic regions of HM-HPMC produced by intermolecular association through long-chain alkyl groups, and with the HM-HPMC molecules themselves, particularly with long-chain alkyl groups. Eventually, the growth of IM crystals is suppressed.

TABLE III. Influence of Polymers on Crystal Growth Rate (*G*)

C_s (μg/g)	*G* (%/°C)		
	Solvent	HM-HPMC	HPMC
3453	83.9 (100)	9.4 (11.2)	44.4 (52.9)
4319	88.4 (100)	12.0 (13.6)	51.6 (58.4)
5181	92.8 (100)	13.2 (14.2)	45.7 (49.2)
6047	97.3 (100)	13.7 (14.1)	46.8 (48.1)

Values in parentheses are % for *G* value of solvent.

Effects of Long-Chain Alkyl Groups of HM-HPMC on Stabilizing Supersaturated Solutions To assess the involvement of the long-chain alkyl groups of HM-HPMC in the stabilization of supersaturated IM solutions, the solubility of IM in supersaturated solutions containing HM-HPMC having various numbers of long-chain alkyl groups was measured. Solubility increased with this number, particularly so with the concentration of the polymer (Fig. 11). The introduction of long-chain alkyl groups into HPMC may thus increase the stabilizing activity, due possibly to increased hydrophobic interactions between long-chain alkyl groups and IM molecules. Examination should also be conducted when hydrophobic association through long-chain alkyl groups is strong due to a higher polymer concentration (0.05—0.6%) or a more hydrophilic solvent than in Fig. 11. The solubility of IM in the presence of a polymer was higher than in its absence. Solubility increased with polymer concentration, though in the case of HM-HPMC, not at polymer concentrations of 0.25% and higher (Fig. 12a). In HM-HPMC solution, a critical point (around 0.25%) was evident from a plot of viscosity *vs.* polymer concentration (Fig. 12b). Below this point, HM-HPMC and HPMC had similar viscosity profiles, but HM-HPMC showed a significant increase in

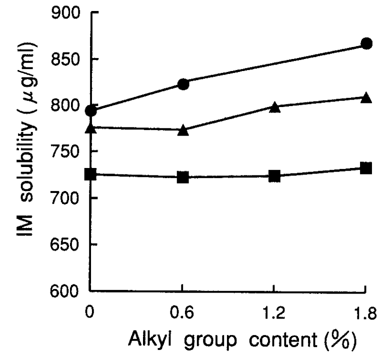

Fig. 11. Influence of Alkyl Group Content on IM Solubility in Supersaturated Solutions

Polymer concentration: —●—, 0.020%; —▲—, 0.010%, —■—, 0.005%. Solvent composition: 0.02 M phosphate buffer solution (pH 4.0) : isopropanol : methanol = 3 : 1 : 0.674 (w : w : w).

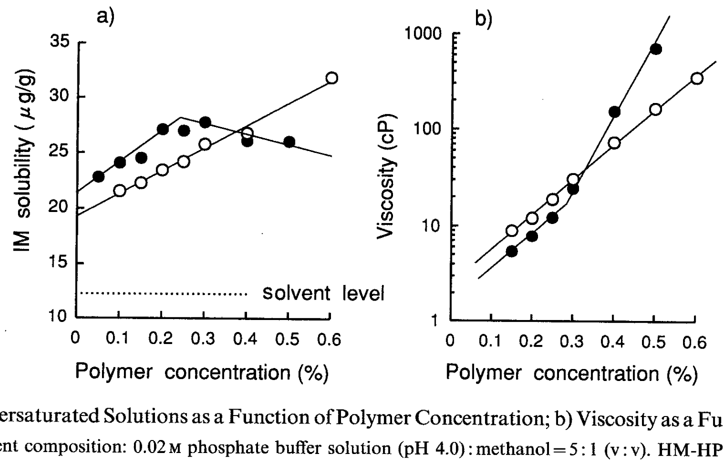

Fig. 12. a) IM Solubility in Supersaturated Solutions as a Function of Polymer Concentration; b) Viscosity as a Function of Polymer Concentration

●, HM-HPMC; ○, HPMC. Solvent composition: 0.02 M phosphate buffer solution (pH 4.0) : methanol = 5 : 1 (v : v). HM-HPMC; alkyl group content 0.6%.

viscosity above that point. Intermolecular hydrophobic association through long-chain alkyl groups may have occurred above the critical point, with the consequent formation of three-dimensional network structures. These results (Fig. 12a, b) suggest that IM is prevented from precipitating when IM and hydrophobic regions of the polymer, particularly long-chain alkyl groups, interact; and the strong intermolecular hydrophobic association (above 0.25%) may render IM molecules incapable of penetrating further into the hydrophobic regions of HM-HPMC.

Conclusion

In supersaturated IM solutions, the solubility of IM in a solution containing HM-HPMC is maintained higher than that in the solvent. This is not due to a suppression of the transformation of IM crystals from α to γ. HM-HPMC greatly suppresses crystal growth, although it slightly accelerates nucleation, leading effectively to the suppression of crystal precipitation. This activity is derived from the original polymer, HPMC, but newly introduced long-chain alkyl groups increase hydrophobic interactions between the polymer and IM molecules, with a consequent greater suppression of crystal deposition. However, the strong intermolecular hydrophobic association of HM-HPMC molecules themselves through long-chain alkyl groups makes IM molecules incapable of interacting further with the hydrophobic regions of HM-HPMC.

References

1) Part III of a series on "Applications of Hydrophobically-Modified Hydroxypropyl Methylcellulose to Topical Preparation." Part I: Ref. 2*a*. Part II: Ref. 2*b*.
2) *a*) I. Saitoh, K. Ikeda, M. Takehara, Y. Takagishi, S. Obara, H. Muto, *Yakuzaigaku*, **52**, 272 (1992); *b*) *Idem*, *ibid.*, **52**, 280 (1992).
3) H. Yamamoto, *Chem. Pharm. Bull.*, **16**, 17 (1968).
4) N. Kaneniwa, M. Otsuka, J. Ichikawa, T. Hayashi, O. Umezawa, *Yakugaku Zasshi*, **107**, 308 (1987).
5) N. Kaneniwa, M. Otsuka, T. Hayashi, *Seyakukojo*, **5**, 738 (1985).
6) S. Y. Lin, *J. Pharm. Sci.*, **81**, 572 (1992).
7) A. Hasegawa, R. Kawamura, H. Nakagawa, I. Sugimoto, *Yakugaku Zasshi*, **105**, 586 (1985).
8) M. C. van der Leeden, D. Verdoes, D. Kashchiev, G. M. van Rosmalen, "Advances in Industrial Crystallization," ed. by J. Garside, R. J. Davey, A. G. Jones, Butterworths, London, 1991, p. 31; M. C. van der Leeden, D. Kashchiev, G.M.van Rosmalen, *J. Colloid Int. Sci.*, **152**, 338 (1992).
9) J. W. Mullin, M. Chakraborty, K. Mehta, *J. Appl. Chem.*, **20**, 367 (1970).
10) J. Nývlt, *J. Crystal Growth*, **3**, **4**, 377 (1968).
11) K. Uekama, K. Ikegami, Z. Wang, Y. Horiuchi, F. Hirayama, *J. Pharm. Pharmacol.*, **44**, 73 (1992).