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Effect of nicotinamide on the properties of aqueous HPMC solutions

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Abstract

The effect of nicotinamide on the properties of aqueous hydroxypropylmethylcellulose (HPMC) solutions was studied. Rheological studies showed that solutions of HPMC of concentration less than 3.0 w/v.% did not form gels and exhibited Newtonian flow patterns at 25 °C. The inclusion of nicotinamide increased the viscosity of HPMC solutions, which indicates that nicotinamide expanded the HPMC coils in aqueous solution. When the temperature of the solutions was raised, they formed gels that were detected by viscometry and oscillation tests as abrupt increases in viscosity, storage modulus and loss modulus and an abrupt decrease in loss angle. Nicotinamide exhibited a salting in effect on the HPMC solutions resulting in an increase in gelation temperatures and cloud points. These effects are considered to be due to the hydrogen-bonding of nicotinamide to HPMC molecules, which was suggested by a shift to a longer wavelength of the UV spectra of aqueous nicotinamide solutions by the addition of HPMC. These results suggested that nicotinamide has affinity with the hydrophilic groups of HPMC.

Keywords: Nicotinamide; Hydroxypropylmethylcellulose; Viscosity; Gelation temperature; Cloud point

1. Introduction

Solid dispersions have been extensively investigated for improving the dissolution properties of poorly water-soluble drugs (Ford et al., 1986; Dordunoo et al., 1996; Rouchotas et al., 2000). Nicotinamide is well known to increase the solubilities of drugs such as nifedipine, indomethacin and halofantrine when formed as solid dispersions with these drugs (Bogdanova et al., 1998; Lim and Go, 2000). Suzuki and Sunada (1997, 1998) found that a combination of nicotinamide and hydroxypropylmethylcellulose (HPMC) improved the dissolution properties of nifedipine and nitrendipine. In spite of the potential of this combined carrier, the influence of nicotinamide on the properties of aqueous HPMC solutions has yet to be fully investigated.

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Recently, Hino and Ford (2001) reported the thermal behaviour of the HPMC-nicotinamide binary mixture. In the fused mixture, HPMC and nicotinamide formed hydrogen bonds and the ratio of the former to latter compound as a complex was ~ 0.59 ($= 0.37/0.63$) by weight. This ratio was consistent with the theoretical ratio at which nicotinamide molecules hydrogen-bonded with hydroxy and hydroxypropoxyl groups of HPMC. In the present paper, we report the effect of nicotinamide on the properties of aqueous HPMC solutions to evaluate their interactions in any potential solid dispersed system containing both entities following exposure to water.

2. Materials and methods

2.1. Materials

Reagent grade nicotinamide was obtained from BDH Laboratories (Poole, UK). HPMC (HPMC 2910) was Methocel E5 premium EP (Colorcon, Dartford, UK). The percentages of methoxyl and hydropropoxyl substitutions are 28–30 and 7–12%, respectively (Ford, 1999). These materials were used without further purification.

2.2. UV-spectroscopy

UV spectra of 0.001 w/v.% nicotinamide aqueous solutions in various concentrations of HPMC (0, 0.03, 0.06 and 0.09 w/v.%) were obtained using a Hewlett Packard 8452A Diode Array spectrophotometer. The spectra of HPMC solutions of corresponding concentrations were subtracted from the spectra of the solutions contains nicotinamide.

2.3. Viscosity of aqueous HPMC-nicotinamide solutions

The required weight of HPMC was hydrated with water, in a refrigerator for 15 h, and further water added to adjust HPMC concentration to 5.0 w/v.%. Aqueous HPMC-nicotinamide solutions were prepared by dilution of this 5 w/v.% solution. The concentrations of HPMC were 1.0–3.0 w/v.% and those of nicotinamide were 0, 1.5 or 3.0 w/v.%. The viscosities of aqueous HPMC-nicotinamide solutions at 25 °C were determined by cone-and-plate viscometry with a CSL^2_{500} Carri-Med rheometer (TA Instrument, New Castle, USA). The diameter and angle of the acrylic cone used were 4 cm and 2°, respectively. The solutions were sheared at 2 Pa for 1 min and then the shear rate was increased and decreased at constant acceleration from 0 to 1000 s^{-1} (up curve) and from 1000 to 0 s^{-1} (down curve), respectively. Both curves took 5 min and 25 data points were used for calculation of viscosities.

2.4. Gelation temperature of HPMC-nicotinamide solutions

Gelation temperatures of aqueous HPMC-nicotinamide solutions were determined by two methods, i.e. viscosity measurement (Method 1) and dynamic viscoelasticity (Method 2) using the Carri-Med viscometer (Section 2.3). The concentrations of HPMC were 1.0–3.0 w/v.% and those of nicotinamide were 0, 1.5 or 3.0 w/v.%.

Method 1: Solutions were sheared at a constant stress, 2 Pa for 5 min at 20 °C to obtain a steady shear state. Subsequently, they were sheared at a constant shear rate, 0.5 s^{-1}, and the temperature was increased gradually from 20 to 80 °C over 30 min. Gelation temperature was defined as the onset temperature when the viscosity increased abruptly.

Method 2: In preliminary experiments, a 1.5 w/v.% HPMC aqueous solution was oscillated at 1 Hz under gradually increased shear stress of 0.01–50.0 Pa over 4 min at 25 °C. G' (storage modulus), G'' (loss modulus) and $\tan\delta$ (δ; loss angle) were almost constant at 0.76–50.0 Pa. Subsequently, the 1.5 w/v.% HPMC aqueous solution was oscillated at gradually increased frequency, 0.01–25 Hz over 13 min under a stress of 2 Pa at 25 °C. G', G'' and $\tan\delta$ were almost constant at 0.01–5.2 Hz. Consequently, the following experiments were carried out.

Solutions were sheared at 2 Pa for 5 min at 20 °C to achieve a steady shear state followed by oscillation at 1 Hz under a constant shear stress, 2 Pa, with gradual increase in temperature from 20

to 86 °C over 33 min. Gelation temperature was defined as the onset temperature when abrupt increase in G' or G'' or abrupt decrease in tan δ occurred.

2.5. Measurement of cloud points

Aqueous HPMC-nicotinamide solutions were poured into disposable cuvettes (pathlength; 1 cm). The cuvettes were placed in a water bath with a temperature regulator (W38, Grant Instruments, Cambridge, UK) and the temperature gradually increased. Initially readings were taken at 1 °C intervals which were reduced to 0.1 °C increments near the cloud points. The cuvette was removed from the water bath and its surface was wiped immediately. Subsequently the light transmission of the sample was measured spectrophotometrically at 800 nm by a CE2021 spectrophotometer (CECIL, Cambridge, UK). The cloud point was defined as the temperature at which the light transmission was 50% of the transmission at room temperature (Mitchell et al., 1990; Sarkar and Walker, 1995).

3. Result and discussion

3.1. Interaction of nicotinamide and HPMC in aqueous solutions

Changes in the UV spectra of nicotinamide caused by the presence of HPMC are shown in Fig. 1. Although a distinct isosbestic point was not detected, decrease in absorbance in the region of 190–208 nm with increase in concentration of HPMC was observed. The absorbance peak shifted to a longer wavelength with increase in the concentration of HPMC. These results indicate possible molecular interaction between nicotinamide and HPMC in aqueous solution. Hino and Ford (2001) reported that hydrogen bonding occurred in their fused binary systems. Presumably these compounds formed hydrogen bonds in aqueous solution. In the solid binary system, the ratio of HPMC:nicotinamide at which HPMC was saturated was ~ 0.59 by weight. The ratio, 0.59 is the theoretical value at which all nicotinamide molecules appear to hydrogen-bond with all hydrophilic groups in HPMC molecules (Hino and Ford, 2001). However, the UV spectra of nicotinamide in aqueous solution varied with change in the concentration of HPMC even when the concentration of HPMC was as high as 0.09%. At this concentration the ratio of HPMC:nicotinamide was 90:1. The reason why the UV spectrum of nicotinamide continued to change with variation in concentration of HPMC was probably due to the exchange of hydrogen bonds from these compounds to solvent (water) molecules and vice versa. This ensured that a constant ratio, equivalent to that seen in the solid state where a saturation of hydrogen bonding between the molecules was reported (Hino and Ford, 2001), could not be obtained in aqueous solution.

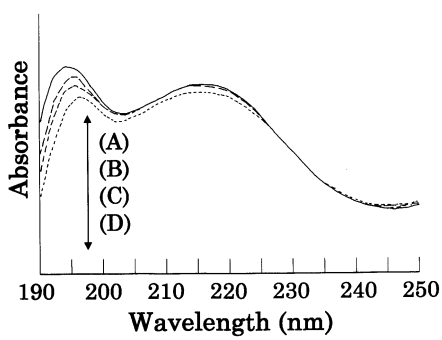

Fig. 1. UV spectra of nicotinamide solutions. Concentration of nicotinamide; 0.001%. Concentration of HPMC: (A) 0; (B) 0.03; (C) 0.06; and (D) 0.09%.

3.2. Viscosities of HPMC-nicotinamide solutions

Rheograms of aqueous HPMC-nicotinamide solutions were studied. Neither obvious hysteresis loops nor distinct yield values of shear stress were observed. When shear stress data (S) were expressed by Eq. (1), the parameter, b, was $0.96 < b < 1.10$ (correlation coefficient, $r > 0.939$).

$$S = aD^b \quad (1)$$

where D is shear rate. Parameters, a and b, are constants related to the viscosity coefficient and flow patterns, respectively.

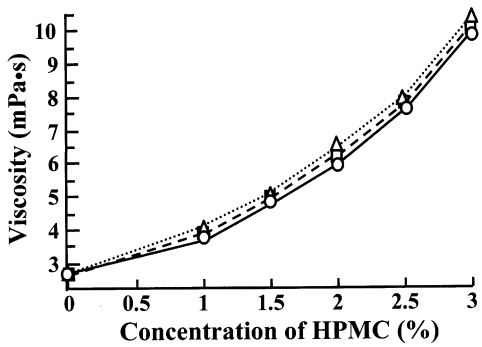

Fig. 2. Apparent viscosity of HPMC-nicotinamide aqueous solution. Concentration of nicotinamide: ○, 0 w/v.%; □, 1.5 w/v.%; and △, 3.0 w/v.%.

When $b > 1$, $b = 1$ and $b < 1$, the flow patterns denote dilatant, Newtonian and thixotropic patterns, respectively. The parameter, b, was close to unity and the Newtonian equation, i.e. Eq. (2), where, η is an apparent viscosity of the solution, was applicable for the solutions ($r > 0.949$). The parameter, a, was similar to the apparent viscosity (represented in Fig. 2) and increased with increase in the concentrations of HPMC and nicotinamide.

$$S = \eta D \tag{2}$$

These results show that structural viscosity (i.e. the phenomena that the viscosity depends on the shear stress) was not considerable under the experimental conditions; i.e. a concentration of HPMC ≤ 3.0 w/v.% and temperature at 25 °C. In other words, a gel was not formed under these conditions.

The apparent viscosities of aqueous HPMC-nicotinamide solutions are shown in Fig. 2. The apparent viscosities of nicotinamide aqueous solution (0, 1.5 and 3.0 w/v.%), η_0, were almost constant ($2.65 \times 10^{-3} - 2.68 \times 10^{-3}$ Pa·s) irrespective of the concentration of nicotinamide. The viscosities of aqueous HPMC solutions increased with increase in the concentration of nicotinamide [$P < 0.05$, 2-dimensional analysis of variance (ANOVA)]. Specific viscosities, η_{sp} ($= \eta/\eta_0 - 1$), were plotted against the concentrations of HPMC (data not shown) and reduced viscosities were calculated as the slopes of the regression lines drawn from the origin (equivalent to η_{sp}/c, where c is the concentration of HPMC). Reduced viscosities of HPMC in 0, 1.5 and 3.0 w/v.% nicotinamide solutions were 7.60, 7.80 and 8.04 l/g, respectively. The larger reduced viscosity was due to the larger η value because η_0 was almost constant. The possible mechanisms of the increase in η are expansion of HPMC polymer coils in solution and a bridging effect of neighbouring polymer chains. However, the latter effect might not be significant because the solutions did not show the structural viscosities. Consequently, the larger η indicates an expansion of polymer coils in solution (Hino et al., 2000). Nicotinamide probably expanded the coils of HPMC molecules by hydrogen bonding as suggested by the UV spectra in Fig. 1.

The data of S and D were fitted to Casson's equation (Eq. (3)) (Casson, 1959) ($r > 0.962$, data not shown).

$$S^{1/2} = S_0^{1/2} + \eta_\infty^{1/2} D^{1/2} \tag{3}$$

where, S_0 is the yield value of shear stress. η_∞ is a constant, which denotes the viscosity extrapolated to $D \rightarrow \infty$.

Experimental S_0 values were 4.64×10^{-7} Pa $< S_0 < 9.87 \times 10^{-4}$ Pa. The shear stress used for the calculation of the parameters was 0.03 Pa $< S <$ 11 Pa. The S_0 values were 0.002–3% of the minimum shear stress used for the calculation and consequently S_0 is considered to be negligible. The value η_∞ was similar to η and increased with increase in the concentrations of HPMC and nicotinamide. It confirmed that a gel was not formed under these experimental conditions and HPMC molecules swelled in the aqueous nicotinamide solution.

3.3. Thermal behavior of HPMC-nicotinamide solution

3.3.1. Gelation temperature of HPMC-nicotinamide solution

Viscosity changes with increase in temperature are shown in Fig. 3. An abrupt increase in viscosity was observed in each curve. The onset temperature of this increase is the gelation temperature (Method 1). The temperature was increased by nicotinamide.

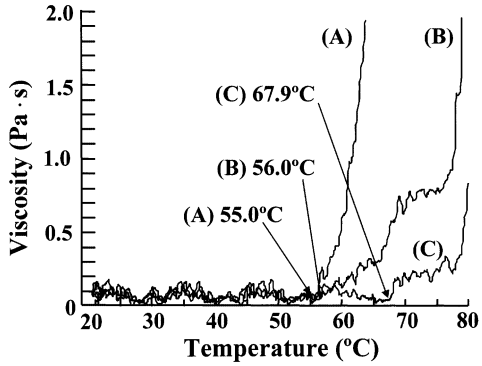

Fig. 3. Change in viscosity of HPMC-nicotinamide aqueous solution with increasing temperature. Concentration of HPMC; 3.0 w/v.%. Concentration of nicotinamide: (A) 0 w/v.%; (B) 1.5 w/v.%; and (C) 3.0 w/v.%. The temperatures denote the gelation temperatures determined by the Method 1.

The gelation temperatures determined by Method 1 are shown in Fig. 4. The temperature increased with increase in the concentration of nicotinamide ($P < 0.001$, 2-dimensional ANOVA). Nicotinamide exhibited a salting in effect on the thermal motion of HPMC molecules.

To study the effect of nicotinamide on the thermal gelation of HPMC solutions in detail, the gelation temperatures were also determined by Method 2 because the viscosities studied in the Method 1 are apparent values that include the overall effects of viscosity and elasticity.

Changes in G', G'' and tan δ of HPMC-nicotinamide solutions with temperature are shown in

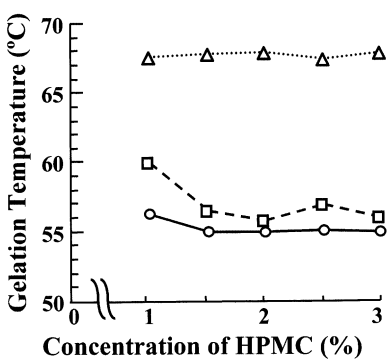

Fig. 4. Gelation temperature determined by Method 1. Concentration of nicotinamide: ○, 0 w/v.%; □, 1.5 w/v.%; and △, 3.0 w/v.%.

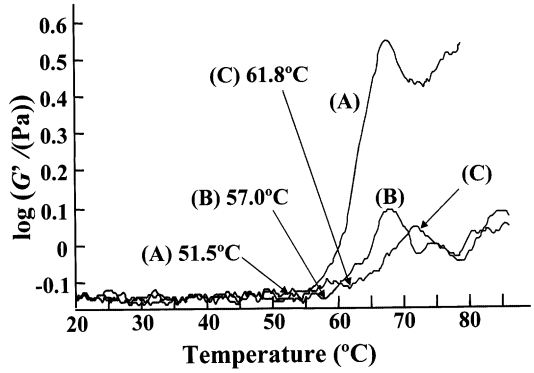

Fig. 5. Change in storage modulus of HPMC-nicotinamide aqueous solution with increasing temperature. Concentration of HPMC; 3.0 w/v.%. Concentration of nicotinamide: (A) 0 w/v.%; (B) 1.5 w/v.%; and (C) 3.0 w/v.%. The temperatures denote the gelation temperatures determined from the change in G'.

Figs. 5–7, respectively. G' and G'' increased and tan δ decreased abruptly with increase in temperature. Gelation temperatures, defined as the abrupt increase or decrease in G', G'' and tan δ values, were similar. G' and G'' values are indices of elasticity and viscosity, respectively. The thermal gelation of HPMC solutions gave abrupt increases in elasticity and viscosity. Gradual slight decrease in G'' was observed at temperatures lower than gelation temperature. This is caused by dehydra-

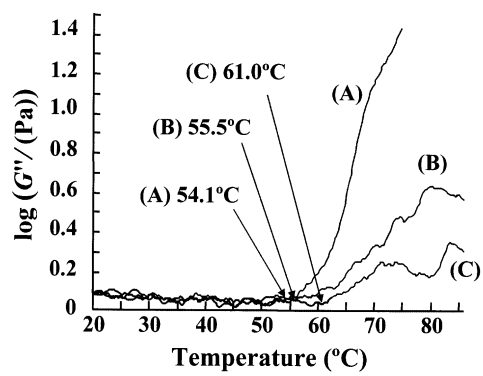

Fig. 6. Change in loss modulus of HPMC-nicotinamide aqueous solution with increasing temperature. Concentration of HPMC; 3.0 w/v.%. Concentration of nicotinamide: (A) 0 w/v.%; (B) 1.5 w/v.%; and (C) 3.0 w/v.%. The temperatures denote the gelation temperatures determined from the change in G''.

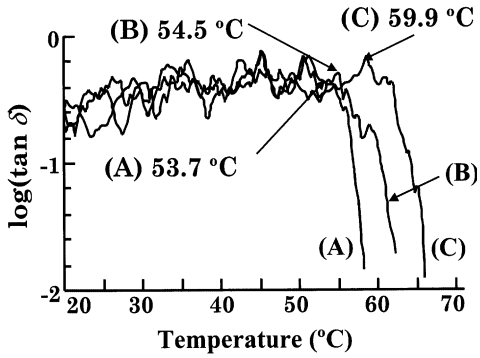

Fig. 7. Change in tan δ of HPMC-nicotinamide aqueous solution with increasing temperature. Concentration of HPMC; 3.0 w/v.%. Concentration of nicotinamide: (A) 0 w/v.%; (B) 1.5 w/v.%; and (C) 3.0 w/v.%. The temperatures denote the gelation temperatures determined from the change in tan δ.

tion of HPMC molecules resulting in the reduction of the volume of the polymer coils and consequent decrease in the viscosity. The parameter, tan δ, is the ratio of G' and G''. Decrease in this value means that the effect of elasticity becomes predominant on the physical properties of the system. Consequently, the thermal gelation of HPMC aqueous solutions gave abrupt increase in viscosity and elasticity and the latter increase was more significant.

Gelation temperature determined by the Method 2 is shown in Fig. 8. Gelation temperatures defined from the change in the three properties were almost same. The temperature increased with increase in the concentration of nicotinamide ($P < 0.001$ for the values determined by measurement of G', G'' and tan δ, 2-dimensional ANOVA). The salting in effect of nicotinamide was also exhibited in Method 2.

Gelation temperatures determined by the two methods are shown in Table 1. Similar results, i.e. the salting in effects of nicotinamide on HPMC solution, were obtained by the two methods. The mechanism of thermal gelation is considered to be due to the aggregation of polymers caused by hydrophobic interactions resulting from the dehydration of cellulose derivative molecules at increased temperature (Sarkar, 1979). Nicotinamide is well known to form hydrogen bonds with many drugs (Bogdanova et al., 1998). Nicotinamide inhibited the dehydration of HPMC molecules presumably by the formation of hydrogen bonds and consequently inhibited entanglement of HPMC molecules resulting in a salting in effect.

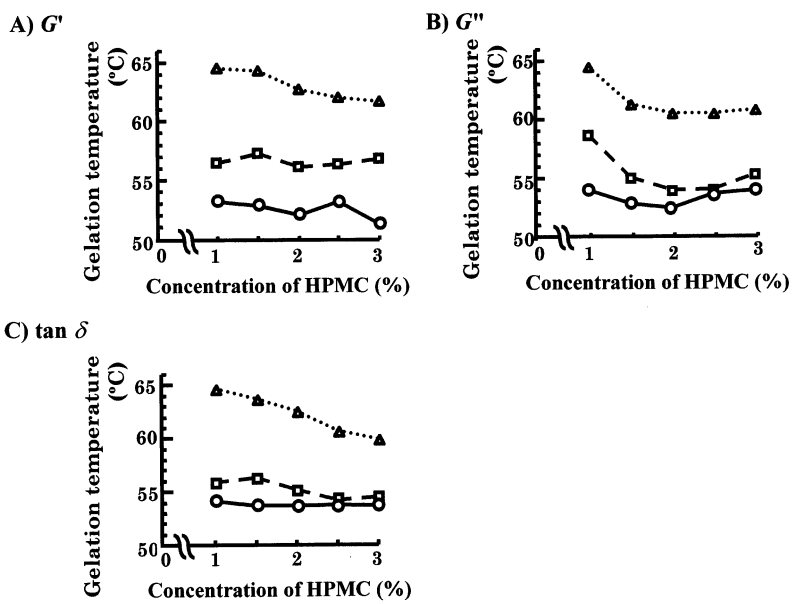

Fig. 8. Gelation temperature determined by Method 2. Gelation temperatures were determined by the change in (A) storage modulus; (B) loss modulus; and (C) tan δ. Concentration of nicotinamide: ○, 0 w/v.%; □, 1.5 w/v.%; and △, 3.0 w/v.%.

Table 1
Gelation temperatures determined by Methods 1 and 2

Method	Parameter	Concentration of HPMC (w/v.%)	Concentration of nicotinamide (w/v.%)		
			0	1.5	3.0
1	η	1.0	56.3	59.9	67.6
		1.5	55.0	56.5	67.8
		2.0	55.0	55.8	67.9
		2.5	55.1	56.9	67.4
		3.0	55.0	56.0	67.9
2	G'	1.0	53.4	56.7	64.7
		1.5	53.0	57.4	64.4
		2.0	52.3	56.3	62.9
		2.5	53.4	56.5	62.2
		3.0	51.5	57.0	61.8
2	G''	1.0	54.1	58.9	64.7
		1.5	53.0	55.2	61.5
		2.0	52.6	54.1	60.7
		2.5	53.8	54.2	60.7
		3.0	54.1	55.5	61.0
2	δ	1.0	54.1	55.9	64.7
		1.5	53.7	56.3	63.7
		2.0	53.7	55.2	62.6
		2.5	53.8	54.2	60.7
		3.0	53.7	54.5	59.9

Gelation temperatures are expressed in °C.

3.3.2. Cloud point of HPMC-nicotinamide aqueous solutions

Cloud points of water-soluble polymers are considered to be indices of decreased solubilities of the polymer with increase in temperature, which are due to dehydration caused by heating. Could points of HPMC-nicotinamide aqueous solutions are shown in Fig. 9. Although the increase in the cloud points by addition of 3 w/v.% nicotinamide were as small as 0.7 °C for both 1.4 and 2.0 w/v.% HPMC solutions, the increase was significant ($P < 0.001$, 2-dimensional ANOVA). The salting in effect of nicotinamide was again confirmed by these results.

The cloudiness of HPMC solutions at the raised temperature is attributed to the same mechanism as the thermal gelation. It was the result of the disruptive effect on the structure of water caused by the polymer-polymer association due to hydrophobic interaction (Haque and Morris, 1993). Nicotinamide inhibited the dehydration of HPMC molecules by hydrogen-bonding to the hydrophilic groups of HPMC molecules, resulting in the protective effect on the structure of water.

In conclusion, nicotinamide exhibited affinity to HPMC molecules presumably by hydrogen-bonding to the hydrophilic groups of HPMC. Consequently, nicotinamide expanded HPMC coils in

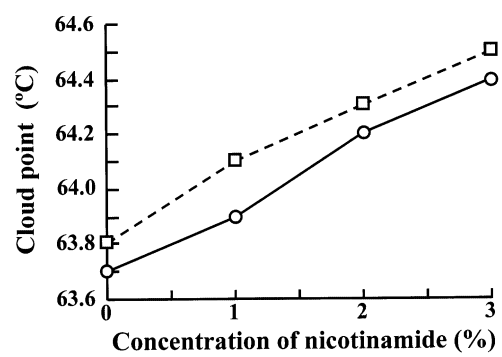

Fig. 9. Cloud point of HPMC-nicotinamide aqueous solution. Concentration of HPMC: □, 1.4 w/v.%; and ○, 2.0 w/v.%.

aqueous solution and exhibited a salting in effect. This molecular affinity presumably improved the dissolution properties of poorly water-soluble drugs by the formation of solid dispersions with a combined carrier of nicotinamide-HPMC (Suzuki and Sunada, 1997), because nicotinamide hydrogen-bonded with drug and HPMC molecules in the solid dispersions and presumably in solutions. After exposing the solid dispersions to aqueous media, nicotinamide expanded HPMC coils and dissolved the drug by hydrogen-bonding, resulting in the supersaturation and enhancement of the dissolution rate of the drug reported in the literature (Suzuki and Sunada, 1997).

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