Colloid Polym Sci 279:1045–1057 (2001)

ORIGINAL CONTRIBUTION

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Influence of polymer structure on the rheological behavior of hydroxypropylmethylcellulose–sodium carboxymethylcellulose dispersions

Received: 17 July 2000
Accepted: 20 November 2000

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Abstract Aqueous dispersions of mixtures of hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose (NaCMC) were prepared in accordance with a two-component simplex lattice design, using polymer varieties with different molecular weights and substitution characteristics. The resulting systems were characterized rheologically by capillary viscometry, flow rheometry, and oscillatory shear techniques, for the determination of kinematic viscosity, index of consistency, index of fluidity, elastic modulus, and viscous modulus. The values obtained for these parameters were fitted with appropriate canonical models, which revealed synergistic effects for some polymer proportions. Maximum synergy was observed when polymer proportions were optimal for the establishment of between-polymer interactions. The synergistic effects on viscosity and elasticity are attributable to the establishment of hydrophobic interactions and hydrogen bonds between HPMC and NaCMC chains, as revealed by IR spectroscopy and modifications in the cloud-point temperature. The observed among-mixture differences in the polymer proportions at which maximum synergy occurs, and the degree of this synergy, are explained by differences in molecular weights and substitution characteristics, and indeed the degree of synergy (as measured by interaction parameters from the fitted canonical models) showed strong dependence on these variables. Microviscosity values, derived from theophylline diffusion data for some of the mixtures, show that the crossover and chain expansion of the polymers in the mixtures (i.e. increased viscosity and elasticity) give rise to a three-dimensional network with greater mesh size and a more hydrophilic microenvironment, favoring solute mobility.

Key words Hydroxypropylmethylcellulose · Sodium carboxymethylcellulose · Synergistic blend · Viscoelasticity · Microviscosity

Introduction

Several recent studies have shown that a useful approach for obtaining aqueous dispersions with appropriate rheological properties for industrial applications is to use polymers of different characteristics, taking advantage of the formation of interpolymer structures [1, 2].

Hydrophilic cellulose derivatives have numerous applications, thanks to their solubility in a wide range of solvents, their thermoplasticity, their surface activity [3], and above all their thickening capacity. This has led to their use as stabilizers of suspensions and emulsions and as excipients for matrix-structure solid drug dosage forms [4]. Mixtures of cellulose ethers, whether ionic or nonionic, offer particularly interesting possibilities for

the development of solid controlled-release oral drug dosage forms, in which, after hydration, the gel layer controls drug release (notably its resistance to drug diffusion and to erosion) [5]. Precise modulation of the mechanisms and the rate of release of diverse drugs can be achieved by appropriate selection of cellulose ethers and their relative proportions [6–9]. This behavior has been attributed to the different hydration processes undergone by the different components as they enter into contact with the dissolution medium, and/or to the possible establishment of interactions between the chains of the different polymers [8, 9], modifying the gel characteristics. However, a more rigorous interpretation requires a detailed analysis of the interactions between the polymers in question and of the effects of these interactions on the rheological properties of aqueous dispersions of those polymers.

There have been several studies of interactions in aqueous media between cellulose derivatives and surfactants [10, 11], but interactions between cellulose derivatives have received less attention [12]. The available theoretical models do not allow accurate prediction of the viscosity of polysaccharide mixtures, though special mention is due to the equations developed by Mannion and coworkers [13, 14] from the model of Morris et al. [15]. The standard procedure for evaluating the formation of cellulose-derivative interpolymer networks is to use flow viscometry to monitor the thickening capacity of dispersions prepared from the different components [12, 16]. However, this technique supplies very limited information on the rheological properties of the system, and the results are frequently difficult to relate to other system properties [4, 8]. Furthermore, some polymeric systems show a lack of correlation between viscosity and the rate of diffusion of small particles or molecules, suggesting a need to consider microviscosity (i.e. viscosity on microscopic spatial scales) [17–19].

In the present study, we investigated the influence of the structural characteristics and water-interaction behavior of hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose (NaCMC) on the rheological properties of mixtures of these two polymers. To this end, we selected and characterized several varieties of HPMC and NaCMC, with different substituents and molecular weights. In accordance with a simplex lattice design, we then prepared aqueous dispersions in which we studied intermolecular interactions and evaluated viscosity, elasticity, and microviscosity.

Experimental

Materials

Anhydrous theophylline was from Sigma (batch 97F-0733). The HPMCs Methocel E4M (batch 87061702, nominal viscosity 4000 mPas), K4M (batch MM87050902 K, nominal viscosity 4000 mPas), and K15M (batch 89110712, nominal viscosity 15000 mPas) were from Dow Stade (Spain). The NaCMCs were from Sigma (NaCMC I, batch 71H0397, nominal viscosity 400–800 mPas), Escuder (NaCMC II, batch 012, nominal viscosity 1000 mPas), and Panreac (NaCMC III, batch 149556940, nominal viscosity 1500–3000 mPas).

Characterization of the polymers

Degree of substitution

The substitution patterns of the various batches were evaluated by ^{13}C NMR spectroscopy of their hydrolysates, as follows [20]. First, 1.0 g polymer was added to 30 ml 6 M sulfuric acid and the mixture was stirred for 1.5 h at 20 °C. The mixture was then made up to 90 ml with deionized water, autoclaved at 2 atm (120 °C) for 1 h, allowed to cool to room temperature, neutralized with barium carbonate, filtered, and concentrated to 2 ml in a rotary evaporator at 40 °C. A sample (1 ml) was then made up to 2 ml with D_2O and centrifuged at 3575*g* for 5 min; 1 ml of the resulting supernatant was analyzed by NMR using a Bruker AMX-300 apparatus at 75 MHz. All shifts were referred to external chromium(III) acetylacetonate in dimethylsulfoxide (3 g/l) at 40 ppm. The spectra were interpreted, and the degree of substitution and molar substitution were estimated as described by Lee and Perlin [21] and Tezuka et al. [22].

Intrinsic viscosity and mean molecular weight

The molecular weights were estimated from the intrinsic viscosities of the polymers. Stock 1% polymer dispersions were obtained by the procedure outlined in USP23-NF18 [23] and diluted with purified water (HPMCs) or 0.1 M NaCl (NaCMCs) to afford a series of dilute dispersions. The kinematic viscosities of these dispersions were measured in sextuplicate at 20 (HPMCs) or 25 °C (NaCMCs) using a Cannon-Fenske capillary viscometer (ref. 5354/2, Afora). Martin's model was then fitted to these data [24] in order to obtain intrinsic viscosities ($[\eta]$). Mean molecular weights were then estimated from the $[\eta]$ values using the Mark–Houwink equation with constants K and a set to 3.39×10^{-4} and 0.88 for the HPMCs [25] and to 1.23×10^{-4} and 0.91 for the NaCMCs [4]. The critical overlap concentration (c^*) was estimated as $1/[\eta]$ [15].

Heat of hydration-solution

The enthalpy of hydration of each polymer at 25 °C was determined in duplicate in a Tronac 458 isoperibol microcalorimeter (Tronac, Utah, USA) consisting of a 50-ml reaction vessel immersed in a thermostatted, insulated water bath. The test sample (0.09–0.11 g) was sealed in a thin-walled glass ampoule and mounted on a rotating support. After thermal equilibration, the ampoule was broken by means of a spring-loaded hammer mounted below it. The rise in the temperature of the system was monitored using a thermistor and was later reproduced using a heating coil in the reaction vessel. The enthalpy of hydration was calculated from the applied current and voltage and the heating time.

Preparation and characterization of the polymer dispersions

Preparation of the dispersions

Dispersions of binary mixtures HPMC–NaCMC (2% w/w) were made up by adding the required weight of dry HPMC to hot deionized water under stirring. After 10 min, the required weight of dry NaCMC was added; the mixture was shaken until the polymers had totally dissolved, then left to stand for 24 h at 4 °C.

IR spectroscopy

IR spectra of films obtained by evaporation of HPMC and NaCMC dispersions were recorded using a Bruker IFS 66 V FT-IR spectrometer. To prepare the films, the dispersions were poured into a Teflon frame model and maintained at 40 °C for 24 h. IR spectra were obtained over the range 400–4000 cm^{-1} by the attenuated total reflection technique.

Determination of the cloud point

The cloud point (i.e. the temperature at which the transmittance is half that at room temperature) was determined in 2.0% HPMC and 5/6:1/6 HPMC:NaCMC dispersions by measuring transmittance (800 nm, Shimadzu UV-240, Kyoto, Japan) at increasing temperatures (5 °C steps until close to the cloud point, then 0.2 °C steps) [26].

Rheologic characterization

Capillary viscometry

The macroviscosity of aqueous dispersions of each polymer and the HPMC–NaCMC mixtures was determined in triplicate at 37 °C with Cannon–Fenske capillary viscometers (refs. 5354/8 and 5354/10, Afora).

Rheometry

All determinations were done in triplicate using a Rheolyst AR-1000N rheometer (TA Instruments, Newcastle, UK) equipped with an AR2500 data analyzer and a thermostatted concentric-cylinder adapter. The flow rheograms were adjusted to the Ostwald equation [27]:

$$\eta = m\dot{\gamma}^{n-1} \quad , \tag{1}$$

where η represents the viscosity and $\dot{\gamma}$ the shear rate, and the indices of consistency (m) and fluidity (n) were determined from this equation.

Creep-recovery profiles, the elastic modulus (G'), and the viscous modulus (G'') were determined by oscillatory shear. First, the linear viscoelastic interval was determined with a strain sweep at 1 rad/s. Creep-recovery profiles were then obtained by application of 0.1 Pa for 5 min. Finally, for determination of G' and G'', we performed frequency sweeps over the range 0.05–50 rad/s.

Microviscosity

Preparation of the dispersions

Dispersions of the HPMC:NaCMC binary mixtures were prepared in theophylline solution (200 mg/l) following the procedure described in Preparation of the dispersions. The osmolarity of 50 μl samples of each dispersion was determined in triplicate using an Osmomat 030 (Gonotec) cryoscopic osmometer.

Diffusion assays

Assays for the characterization of theophylline release from the different dispersions were performed in triplicate in Franz–Chien vertical diffusion cells (Vidra Foc, Valencia, Spain) fitted with cellulose acetate membrane filters (0.45-μm pore size) (CA502500, Teknokroma, Barcelona, Spain) between the donor and the recipient compartments. A 2.00-ml sample of the test formulation, at 37 °C, was placed in the donor compartment. The recipient compartment contained 5.50 ml isotonic NaCl solution, thermostatted at 37 °C and stirred with a magnetic rod. The area available for diffusion was 0.785 cm^2. Samples (0.50 ml) were taken from the recipient compartment at intervals over an 8-h period for the determination of theophylline on the basis of absorption at 271 nm (Shimadzu UV-240, Kyoto, Japan); in each case, the recipient medium volume was immediately made up with isotonic NaCl solution. Diffusion coefficients were estimated by fitting the Higuchi [28] equation:

$$\frac{Q}{A} = 2\, c_0 \sqrt{\frac{D\, t}{\pi}} \quad , \tag{2}$$

where Q is the amount of theophylline (milligrams) released by time t (minutes), A is the diffusion area (square centimeters), c_0 is the initial concentration of theophylline in the formulation (grams per liter), and D is the diffusion coefficient (square centimeters per minute).

The microviscosity of these dispersions was then estimated using the Stokes–Einstein relation [17]:

$$D_0/D = \eta/\eta_0 \quad , \tag{3}$$

where D and D_0 are diffusion coefficients (square centimeters per minute) for theophylline in the presence and the absence of polymer, respectively, and η and η_0 are the viscosities (millipascal seconds) of the polymer dispersion (microviscosity) and of the medium without polymer, respectively.

Experimental design and statistical analysis

The composition of the HPMC:NaCMC binary mixtures was chosen following the simplex lattice design shown in Table 1 [29]. To evaluate the possible synergism or antagonism of the rheological properties of the binary mixtures, observed and calculated values were compared. For homologous polymer blends, the calculated apparent viscosity (η_{cal}) was determined by the log-additivity rule [16, 30]:

$$\log \eta_{cal} = x_1 \log \eta_1 + x_2 \log \eta_2 \quad , \tag{4}$$

where x_1 and x_2 are the weight fractions of HPMC and NaCMC, respectively, and η_1 and η_2 are the experimental viscosity of a 2% HPMC dispersion and a 2% NaCMC dispersion, respectively.

The percentage change in viscosity was calculated from the equation of Walker and Wells [16]:

$$(\eta_{obs} - \eta_{cal})100/\eta_{cal} \quad . \tag{5}$$

The log-additivity rule was also applied to the other rheological parameters and to the diffusion coefficients and, in order to compare the degree of synergism between the properties of the HPMC and NaCMC dispersions, the following general first-order canonical mathematical model was applied [29]:

$$\log \beta_{cal} = x_1 \log \beta_1 + x_2 \log \beta_2 \quad , \tag{6}$$

with the coefficients β_1 and β_2 equal to the values of the property in question for the pure HPMC or pure NaCMC dispersion,

Table 1 Simplex lattice design for selection of mixtures of hydroxypropylmethylcellulose (*HPMC*) and sodium carboxymethylcellulose (*NaCMC*) to be characterized

Number	x_1	x_2	%HPMC	%NaCMC
1	0	1	0.0	2.0
2	1	0	2.0	0.0
3	1/2	1/2	1.0	1.0
4	5/6	1/6	1.66	0.33
5	4/6	2/6	1.33	0.66
6	2/6	4/6	0.66	1.33
7	1/6	5/6	0.33	1.66

respectively. The test point was binary mixture 3 (Table 1). If the first-order model was invalid (i.e. gave a poor fit), the second-order canonical equation obtained by inclusion of this point (β_{12}) was used:

$$\log \beta_{cal} = x_1 \log \beta_1 + x_2 \log \beta_2 + x_1 x_2 \log \beta_{12} \quad . \tag{7}$$

When the maximum deviation in the binary mixture was other than at the midpoint, the effect of a cubic term was evaluated:

$$\log \beta_{cal} = x_1 \log \beta_1 + x_2 \log \beta_2 + x_1 x_2 \log \beta_{12} + (x_1 - x_2) x_1 x_2 \log \phi_{12} \quad . \tag{8}$$

In this case, the model coefficients were estimated by a least-squares nonlinear regression. To decide whether to use the second-order canonical model or the cubic model, we calculated the Akaike information criterion (AIC) [31]:

$$AIC = N \ln RSS + 2p \quad , \tag{9}$$

where N is the total number of data points, RSS the residual sum of squares, and p the number of parameters fitted. In each case, the model selected was that which gave the lowest AIC value.

The influence of polymer properties on the value of β_{12} (Eqs. 7, 8) was assessed by stepwise multiple regression ($\alpha = 0.05$).

Results and discussion

In general, the ionic polymers showed lower degrees of substitution than the nonionic polymers, especially NaCMC-II, which do not present substituents at position 3 (Table 2). HPMC-E4M exhibited a much higher degree of substitution than the other nonionic polymers, owing to its methoxyl groups. In addition, the mean molecular weight showed marked differences within each group of polymers.

The water-interaction behavior of the different polymers was characterized by determination of the heat of hydration-solution and, in the case of the HPMCs, of the cloud-point temperature of 2.0% dispersions. HPMC-E4M was much less hydrophilic than the other HPMCs, this being attributable to its higher methoxyl group content (since these groups are hydrophobic [32]). The NaCMC dispersions remained transparent over the entire temperature interval studied (to 100 °C), owing to the presence of carboxyl groups that hinder chain aggregation due to dehydration and the establishment of hydrophobic interactions responsible for the precipitation of HPMC at increasing temperature [32]. Within each group of polymers, the amount of energy released during the hydration process declines with increasing molecular weight. This may be related to the fact that longer polymer chains require a greater initial energy input to separate them [33].

Once the polymers had been characterized structurally, we prepared aqueous dispersions of polymer mixtures (Table 1) for evaluation of their rheological properties. In all cases, the concentration of each polymer exceeded the critical overlap concentration (c^*, Table 2), and the dispersions obtained were of homogeneous appearance. Figure 1 shows kinematic viscosities obtained by capillary viscometry, together with values predicted by application of the log-additivity rule (i.e. the first-order canonical model) [16, 30]. As can be seen, all of the binary systems showed synergistic effects (i.e. nonideal behavior), though the relative proportions at which such effects were observed varied depending on the component polymers present.

In mixtures of any of the HPMCs and NaCMC-I, and of HPMC-K15M and NaCMC-II, rheological behavior was fitted well by the second-order canonical model, which predicted maximum synergy when the dispersion contained both components in equal amounts. For these dispersions, viscosity increases with respect to viscosities predicted assuming ideal behavior (i.e. by the log-additivity rule) were 39.2% (E4M:NaCMC-I), 40.6% (K4M:NaCMC-I), 79.4% (K15 M-Na-CMC-I), and 38.2% (K15M:NaCMC-II). For the remaining systems, the third-order model proved most accurate (with ϕ_{12} values greater than or equal to those of β_{12}), since synergy appeared with lower proportions of NaCMC, particularly in the 5/6:1/6 HPMC:NaCMC mixtures, in which viscosity increases with respect to viscosities predicted assuming ideal behavior were 23.2% (E4M:NaCMC-II), 25.2% (K4M:NaCMC-II), 48.4% (E4M:NaCMC-III), 34.7% (K4M:NaCMC-III), and 47.8% (K15M:NaCMC-III).

The values of the index of consistency (m) obtained by flow rheometry showed a similar pattern. The values

Table 2 Basic properties of the HPMCs and NaCMCs studied (*DS*: degree of substitution, *ME*: methoxyl, *HP*: hydroxypropoxyl, *CM*: carboxyl, [η]: intrinsic viscosity)

Polymer	DS_2	DS_3	DS_6	DS_T	%ME	%HP	%CM	[η] (dl/g)	c^* (g/dl)	Molecular weight	Heat of solution (J/g)	Cloud point (°C)
E4M	0.89	0.46	0.77	2.13	29.9	8.36	–	8.12	0.123	95,000	56.63	56.2
K4M	0.73	0.23	0.69	1.65	22.9	8.27	–	7.31	0.137	84,200	92.54	70.7
K15M	0.72	0.24	0.73	1.69	23.3	8.62	–	9.31	0.107	111,000	84.12	71.3
NaCMC-I	0.42	0.21	0.40	1.03	–	–	26.1	5.35	0.187	125,000	127.7	–
NaCMC-II	0.31	–	0.40	0.71	–	–	19.8	6.83	0.146	164,000	107.9	–
NaCMC-III	0.43	0.27	0.40	1.10	–	–	28.2	9.89	0.101	245,000	94.45	–

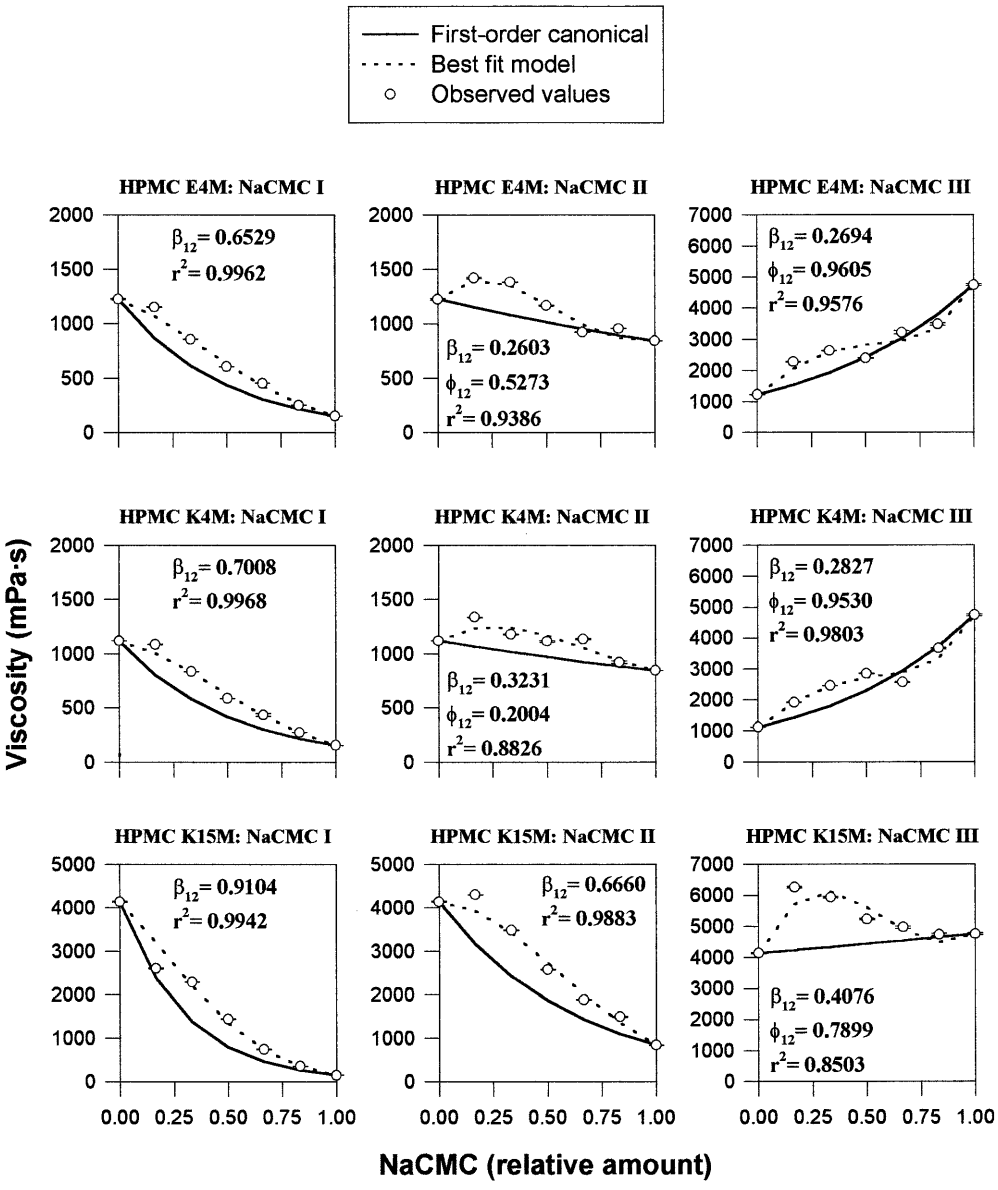

Fig. 1 Kinematic viscosity of the hydroxypropylmethylcellulose (*HPMC*):sodium carboxymethylcellulose (*NaCMC*) mixtures indicated, showing curves predicted by the first-order canonical model (i.e. the log-additivity rule) and by the second- or third-order canonical model (whichever gave the better fit)

of the index of fluidity (n) were, in general, accurately predicted by the log-additivity rule (Fig. 2), except in mixtures containing NaCMC-I, which showed lower n values than predicted.

To investigate the rheological behavior of HPMC:NaCMC mixtures in greater detail, we used oscillatory shear techniques, which were used in recent studies of rheologic synergy in dispersions of ethylhydroxyethylcellulose (EHEC) [11] or HPMC [34] and anionic surfactants. The values of the viscous modulus (G'') and the elastic modulus (G') obtained at an oscillation frequency of 0.9165 rad/s were chosen as representative of system behavior (Figs. 3, 4). As expected, the observed G'' curves obtained were similar to those obtained for the kinematic viscosity as determined by capillary viscometry. The synergy observed in the G' curves for the different mixtures confirms the existence of interactions between the two types of macromolecule, and the formation of interpolymer networks, although the maximum synergy in elasticity occurs at higher proportions of NaCMC than the maximum synergy in viscosity. The second-order canonical equation was the best-fitting model only in the cases of the E4M:NaCMC-III and K4M:NaCMC-III systems, and in the second case the values of G' obtained were practically identical to those predicted by the log-additivity rule. The fact that the maximum synergy in G' occurred at a different proportion of NaCMC to the maximum synergy in G'' may be related to the different conformations adopted by this polyelectrolyte at

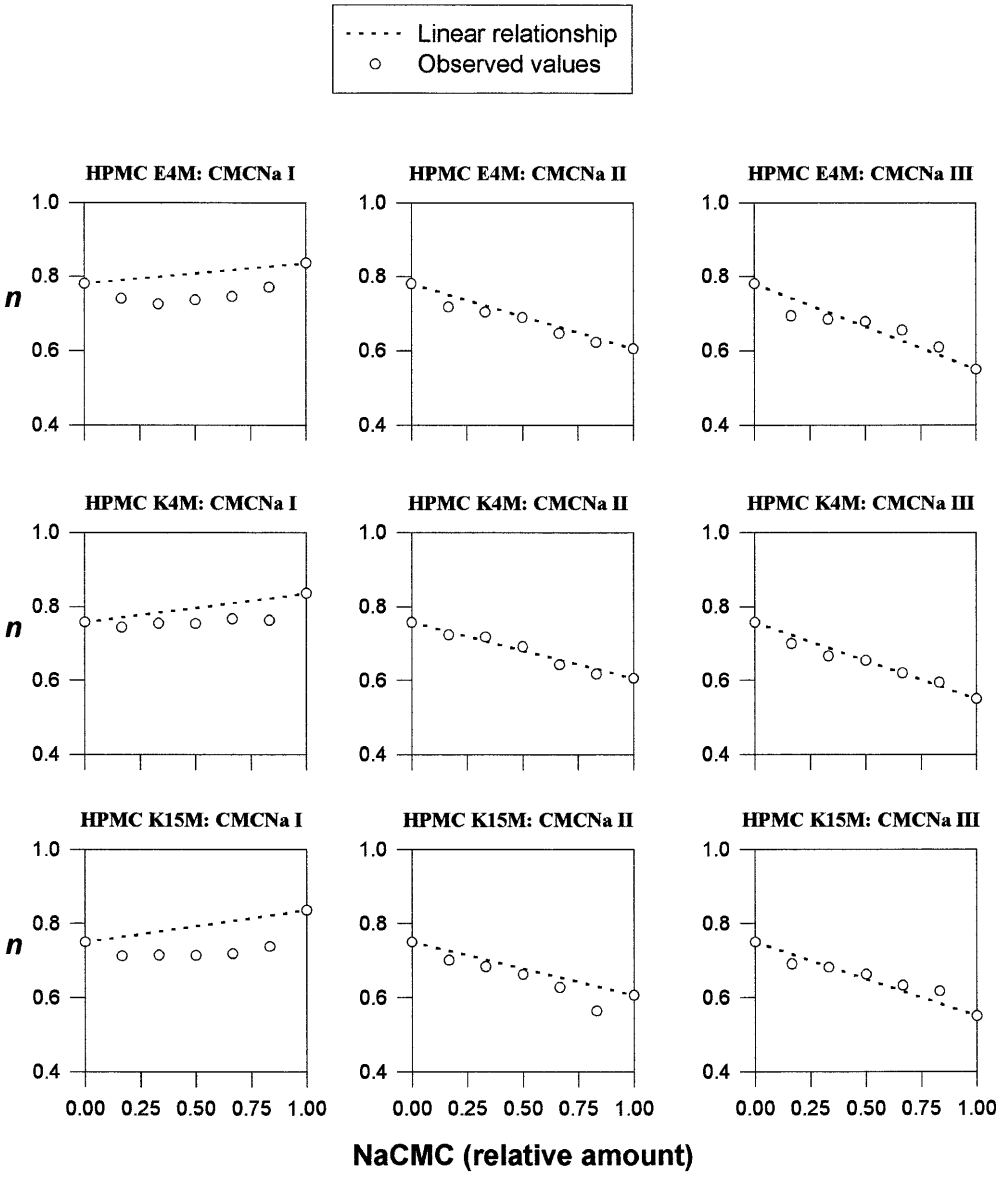

Fig. 2 Values of the index of fluidity (n) obtained from the flow curves for the HPMC: NaCMC mixtures indicated

different concentrations. In experiments with an NaCMC of similar molecular weight, Kästner et al. [35] observed that the polymer chains adopted an extended conformation in highly diluted systems; as the critical overlap concentration was reached, the chains began to overlap, though they retained extended conformation up to a concentration of about 0.5%, beyond which the single-chain end-to-end distance declined as a result of coiling. We found that our aqueous dispersions of NaCMC began to show viscoelastic behavior at this concentration (0.5%) and above. In the case of mixtures, the conformation change could have been expected to give rise to an increase in the density of the polymer network, which would be accompanied by a corresponding increase in G'.

Comparison of the interaction parameters obtained for the kinematic viscosity with each of the mixtures indicates that within each variety of HPMC, β_{12} declines with increasing NaCMC molecular weight and that within each variety of NaCMC, the value of β_{12} is practically the same for mixtures containing E4M and mixtures containing K4M, but is markedly higher for mixtures containing K15M (Fig. 5). The opposite effect is observed with ϕ_{12}.

Regression analysis with the interaction parameters $\beta_{12(G'')}$ or $\beta_{12(G')}$ as dependent variables indicated that $\beta_{12(G'')}$ was strongly influenced not only by molecular weights but also by the methoxyl-group content of the HPMC (%ME), while $\beta_{12(G')}$ was strongly influenced by the carboxyl-group content of the NaCMC (%CM):

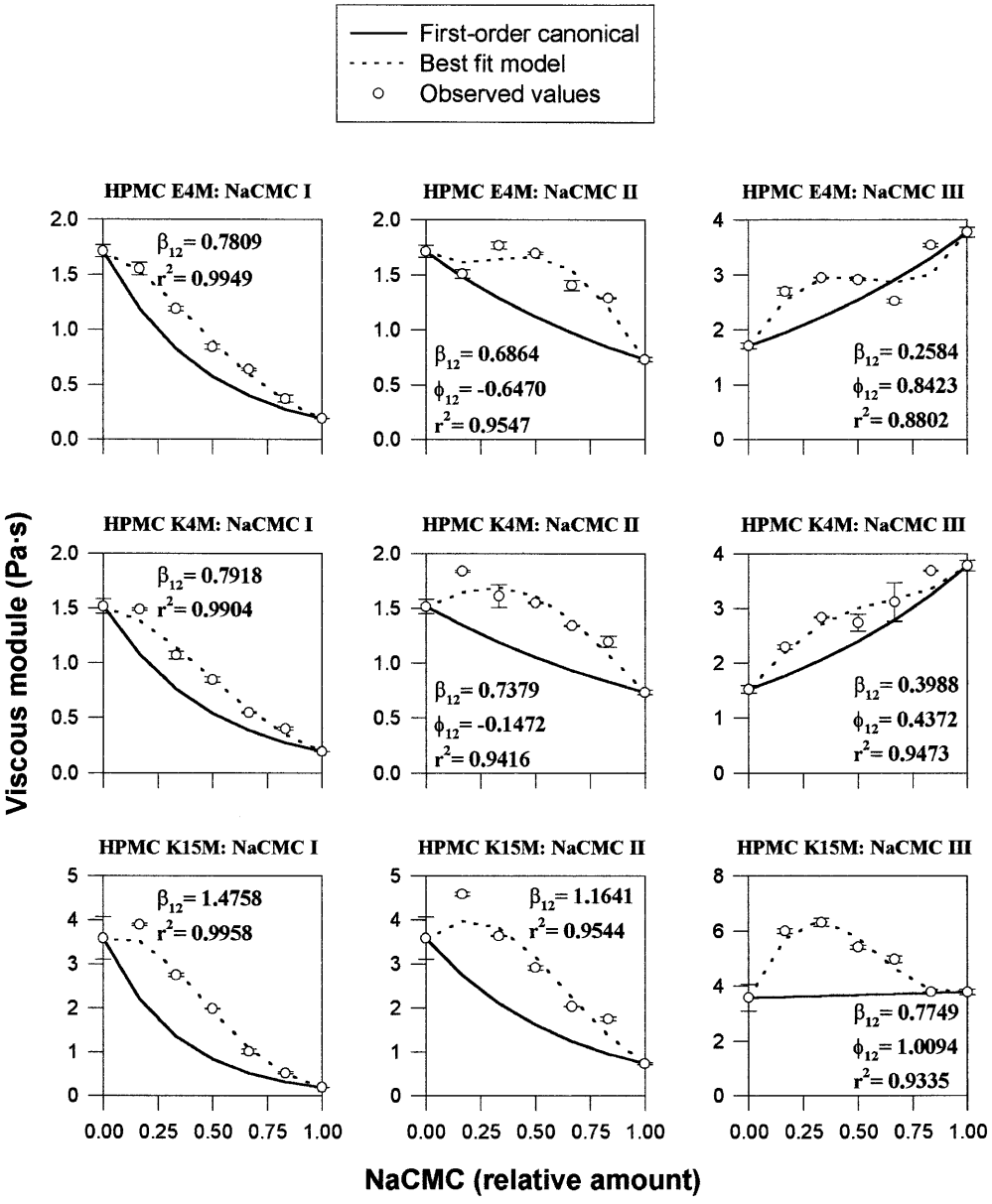

Fig. 3 Viscous moduli of the HPMC:NaCMC mixtures indicated, showing curves predicted by the first-order canonical model (i.e. the log-additivity rule) and by the second- or third-order canonical model (whichever gave the better fit)

$$\beta_{12(G'')} = 2.3 \times 10^{-5}\ \mathrm{MW_{HPMC}} - 4.2 \times 10^{-6}\ \mathrm{MW_{NaCMC}} - 0.027\%\ \mathrm{ME};$$
$$r^2 = 0.9877[F_{(3,6)} = 214.0, \alpha < 0.01]\ , \quad (10)$$

$$\beta_{12(G')} = 2.9 \times 10^{-5}\ \mathrm{MW_{HPMC}} - 2.6 \cdot 10^{-6}\ \mathrm{MW_{NaCMC}} + 0.14\%\ \mathrm{CM};$$
$$r^2 = 0.9890[F_{(3,6)} = 239.9, \alpha < 0.01]\ . \quad (11)$$

As can be seen from these equations, the molecular weights of the two polymers have similar effects on both interaction parameters. In mixtures prepared with the two HPMCs of most similar molecular weight, E4M and K4M (Fig. 3), the decline in the value of $\beta_{12(G'')}$ is accompanied by a marked increase in the absolute value of ϕ_{12}, indicating that a higher methoxyl-group content facilitates interaction with hydrophobic groups of other chains, leading to the formation of a larger number of physical cross-links [16]. The dependence of $\beta_{12(G')}$ on the carboxymethyl-group content (note, for example, that mixtures prepared with NaCMC-I, with a slightly lower molecular weight than NaCMC-II but a higher degree of substitution, show much higher values of both interaction parameters than mixtures containing NaCMC-II; Fig. 4) indicates that the elasticity increases with increasing carboxymethyl-group content.

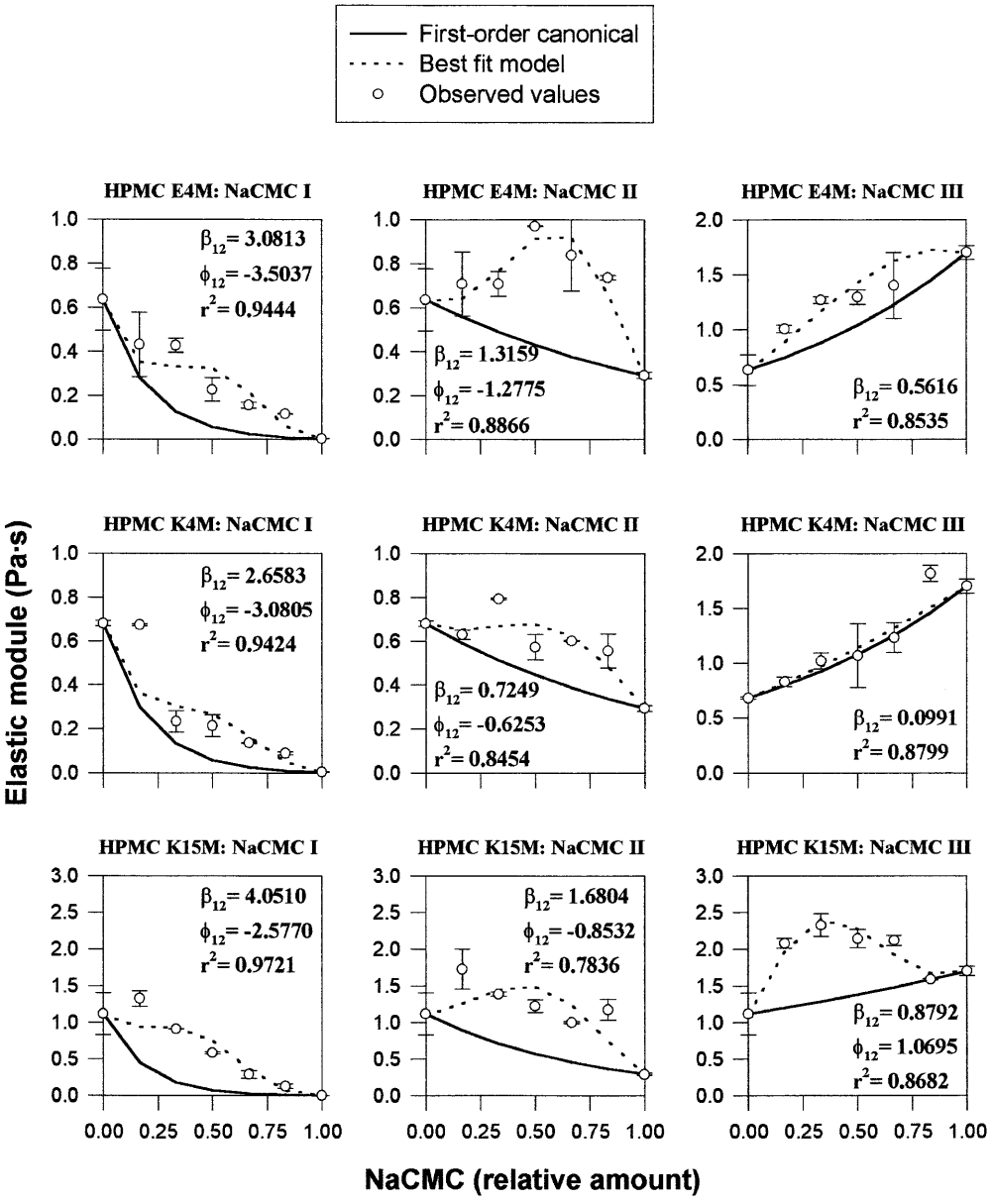

Fig. 4 Elastic moduli of the HPMC:NaCMC mixtures indicated, showing curves predicted by the first-order canonical model (i.e. the log-additivity rule) and by the second- or third-order canonical model (whichever gave the better fit)

With the aim of investigating the role played in these effects by hydrophobic interactions between the polymers making up the mixtures, and by the hydrogen bonds between carboxyl groups of the NaCMCs and hydroxyl groups of the nonionic polymer [14, 16], we obtained IR spectra of films prepared from dispersions of each polymer and its mixtures and determined the cloud-point temperature of 5/6:1/6 HPMC:NaCMC mixtures. As an example, Fig. 6 shows the IR spectra of films obtained from dispersions of K15M, NaCMC-III, and their 1:1 mixture. In the spectra for HPMCs and NaCMCs, a wide band is observed between 3800 and 3000 cm^{-1}, corresponding to O–H stretching and indicating that the hydroxyl groups are not free but form hydrogen bonds [36]. The C–H bonds of the ring give rise to a band at 2900 cm^{-1}. A band at 2853 cm^{-1} was assigned to symmetric CH_2 stretching, and a band at 1455 cm^{-1} to CH_2 bending [37]. Bands corresponding to methoxyl groups (1200–1185 cm^{-1}) were observed only in the HPMC spectra. Bands corresponding to asymmetric (1605 cm^{-1}) and symmetric (1422 cm^{-1}) C–O stretching in carboxylate ions were observed only in the NaCMC spectra.

The bands due to ether-group C–O–C stretch were very strong in all the spectra, though slightly displaced with respect to the theoretical position (1150–1060 cm^{-1}): absorption peaks were observed at 1055 ± 5 and 1020 ± 5 cm^{-1}, with a minor shoulder

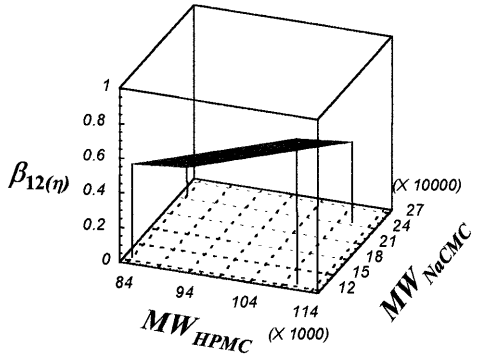

Fig. 5 Plot showing the influence of the HPMC molecular weight and the NaCMC molecular weight on the interaction parameter β_{12} (for kinematic viscosity) ($\beta_{12(\eta)} = 1.1 \times 10^{-5}MW_{HPMC} - 3.1 \times 10^{-6}MW_{NaCMC}$; $r^2 = 0.9431$; $F_{(2,7)} = 66.76$; $\alpha < 0.01$)

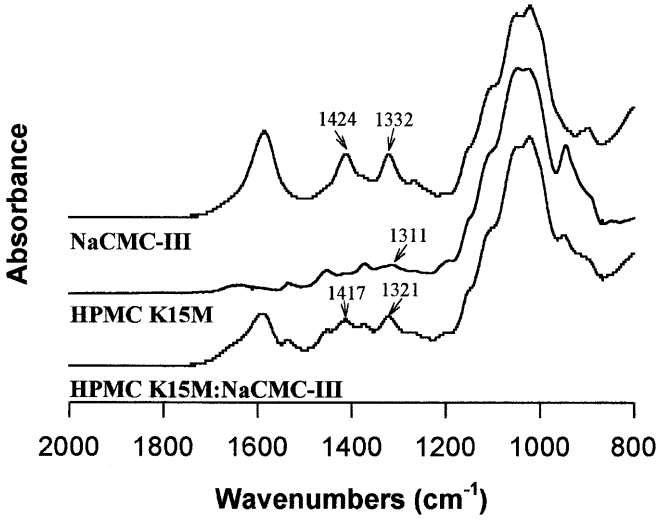

Fig. 6 IR spectra of NaCMC-III, HPMC K15M, and 1:1 HPMC K15M:NaCMC-III films

at 1115 cm^{-1}. This pattern is clearly unlike that observed in the IR spectra of powdered polymers, but is similar to that observed by Ostrovski et al. [38] in the IR spectra of aqueous dispersions of EHEC. These authors attributed this behavior to the increasing mobility of glycosidic bonds (C–O–C) as an increasing proportion of intermolecular and intramolecular hydrogen bonds break. Our results suggest that this greater flexibility is maintained in films.

In the spectra corresponding to the films prepared with 1:1 mixtures of HPMC and NaCMC, the bands present in the spectra for the individual components are practically unaltered. Only one new band is present, corresponding to CH_2 vibrations at 1321 cm^{-1}, and overlapping with those corresponding to CH_2 vibrations in the HPMC spectrum (1311 cm^{-1}) and the NaCMC spectrum (1332 cm^{-1}), whether because of proximity or because of the establishment of hydrophobic interactions between the two types of polymer [39].

In the spectra of 1:1 HPMC:NaCMC films, we also observed a slight shift of the ether-group C–O–C band, to 1020 cm^{-1}, and of the carboxyl-group CH_2 band, to 1417 cm^{-1}. These observations, together with the non-appearance in any of the mixtures of the characteristic bands of ester bonds (at 1700–1725 and at 1270–1150 cm^{-1}), indicate that no strong chemical bond is established between the two polymers and that the interactions between the two are probably of electrostatic and/or hydrophobic type only. Similar results obtained in mixtures of CMC and HEC have been attributed by Zhang [12] to the establishment of hydrogen bonds between the two types of polymer.

The determination of the cloud point allows assessment of whether the incorporation of additives modifies the properties of a nonionic cellulose ether in solution [26]. The values of this parameter obtained for the mixtures studied in all cases proved to be lower than those for 2% HPMC dispersions, despite the fact that these dispersions showed a slightly lower HPMC concentration (1.66%) (55 °C for those containing E4M, and 67.5–68 °C for those containing K4M and K15M), confirming the existence of significant interactions between the two polymers.

In view of these results, the observed effects on the viscosities of the aqueous dispersions of the various mixtures may be attributed to interactions between the two polymers leading to chain crossover and chain expansion owing to the presence of NaCMC ionic groups. The increased polarity of the complex might increase the cloud-point temperature, but the crossover of the chains, the greater hydrophilicity of the NaCMC, and the presence of sodium contraions would facilitate the process of dehydration of the HPMC [26]. In this view, the number and distribution of the substituents and the mean length of the cellulose chains should be key determinants of the appearance of synergistic effects. Note that theoretically for a ratio of 5/6:1/6 HPMC:NaCMC, the number of hydroxypropoxyl and carboxyl groups is almost the same. In addition, the changes provoked by chain crossover will to a great extent depend on the molecular weight of the different polymers (Fig. 5, Eqs. 10, 11). This may be attributable to the relationship existing between the number of hydroxyl or carboxyl groups available and the mean length of the polymer chains. Once an optimal hydroxyl/carboxyl ratio has been reached, the addition of more hydroxyl (or carboxyl) groups will not have any further effect on the degree of synergy, since there are no more carboxyl (or hydroxyl groups) available on the other polymer. This would explain why certain mixtures give rise to viscosity increases with respect to the values predicted by the log-additivity rule, why the proportion of NaCMC required for synergy is lower (as indicated

by lower values of $\beta_{12(\eta)}$, $\beta_{12(G')}$, and $\beta_{12(G'')}$, and higher values of $\phi_{12(\eta)}$, $\phi_{12(G')}$, and $\phi_{12(G'')}$) at higher NaCMC molecular weights, and why the presence in the mixture of NaCMC-II (with a lower carboxyl-group content) induces increases in viscosity lower than those induced by both its lower- and higher-molecular-weight homologues (NaCMC-I and NaCMC-III, respectively).

In addition, the interaction of long HPMC chains with shorter NaCMC chains may mean that expansion of the NaCMC leads to loss of its random-coiled conformation even at high concentrations [12, 35] and to adoption of a more stretched conformation. Additionally, it is undoubtedly also relevant that NaCMC-I, although its molecular weight is not much lower than that of NaCMC-II, has a rather uniform distribution of carboxyl groups, giving rise to greater chain rigidity [35]. This hypothesis is confirmed by the lower index of fluidity of mixtures prepared with NaCMC-I than of mixtures prepared with NaCMC-II, as observed in rotational viscometry (Fig. 2). The higher pseudoplasticity of these mixtures (with respect to dispersions of the individual components) may be attributable to reduced stability of the heteropolymeric network in response to increasing shear force. Similar responses have been observed in mixtures of HEC and poly(acrylic) acid [39] and HEC and CMC [12].

In view of the known influence of the rheological properties of polymer dispersions on the diffusion through them of molecules or small particles, and given that the resistance to flow of such particles may differ from that predicted by capillary viscometry [17–19], we evaluated the possible implications for microviscosity of the synergistic effects detected at the macroscopic level. Several authors have demonstrated the effect of particle size on microviscosity [18], and to avoid this effect we used theophylline, a solute of intermediate molecular size that does not interact with the polymers used [26]. The diffusion coefficient for this solute was estimated in dispersions of each of the polymers and in 5/6:1/6, 1:1, and 1/6:5/6 HPMC:NaCMC mixtures. In all cases, theophylline release was adequately fitted by the Higuchi [28] equation. The diffusion coefficient values obtained are shown in Table 3 and the corresponding microviscosity values are shown in Fig. 7. In general, the 5/6:1/6 HPMC:NaCMC mixture showed the lowest microviscosity values, much lower than those predicted by the log-additivity rule. The remaining mixtures showed microviscosity values that were similar or slightly lower than predicted values, except for HPMC-K15M:NaCMC-II mixtures, which showed microviscosities higher than the predicted values. The lowest microviscosity values are displayed by mixtures containing more HPMC than NaCMC (i.e. those mixtures that display most marked synergy in apparent viscosity and viscous modulus), suggesting that apparent viscosity and viscous modulus respond differently to the interactions between

Table 3 Theophylline diffusion coefficients (cm^2/min) in dispersions of the different HPMC:NaCMC mixtures at the proportions indicated. The values shown are means (standard deviations) of six determinations. $D_0 = 4.5 \times 10^{-3}$ cm^2/min

NaCMC Proportion	HPMC E4M + NaCMC			HPMC K4M + NaCMC			HPMC K15M + NaCMC		
	I	II	III	I	II	III	I	II	III
0/6	7.712×10^{-4}	7.712×10^{-4}	7.712×10^{-4}	7.031×10^{-4}	7.031×10^{-4}	7.031×10^{-4}	5.049×10^{-4}	5.049×10^{-4}	5.049×10^{-4}
	(2.033×10^{-5})	(2.033×10^{-5})	(2.033×10^{-5})	(1.697×10^{-5})	(1.697×10^{-5})	(1.697×10^{-5})	(1.334×10^{-5})	(1.334×10^{-5})	(1.334×10^{-5})
1/6	1.802×10^{-3}	1.194×10^{-3}	1.085×10^{-3}	1.444×10^{-3}	1.222×10^{-3}	1.039×10^{-3}	1.236×10^{-3}	8.123×10^{-4}	7.688×10^{-4}
	(2.662×10^{-5})	(6.139×10^{-5})	(1.123×10^{-4})	(2.031×10^{-5})	(3.788×10^{-5})	(1.031×10^{-6})	(3.762×10^{-6})	(2.393×10^{-5})	(1.828×10^{-5})
3/6	1.288×10^{-3}	1.083×10^{-3}	9.037×10^{-4}	9.816×10^{-4}	8.575×10^{-4}	7.341×10^{-4}	1.063×10^{-3}	4.812×10^{-4}	6.304×10^{-4}
	(1.582×10^{-5})	(2.339×10^{-5})	(9.862×10^{-6})	(3.208×10^{-5})	(3.909×10^{-5})	(4.444×10^{-5})	(3.519×10^{-5})	(2.121×10^{-5})	(1.121×10^{-5})
5/6	1.473×10^{-3}	9.729×10^{-4}	6.712×10^{-4}	1.742×10^{-3}	1.022×10^{-3}	7.421×10^{-4}	1.433×10^{-3}	7.285×10^{-4}	7.241×10^{-4}
	(9.140×10^{-5})	(1.538×10^{-4})	(4.786×10^{-5})	(5.317×10^{-5})	(8.454×10^{-5})	(4.304×10^{-5})	(1.422×10^{-5})	(4.149×10^{-5})	(3.559×10^{-5})
6/6	2.145×10^{-3}	1.148×10^{-3}	5.966×10^{-4}	2.145×10^{-3}	1.148×10^{-3}	5.966×10^{-4}	2.145×10^{-3}	1.148×10^{-3}	5.966×10^{-4}
	(2.156×10^{-5})	(6.932×10^{-6})	(3.762×10^{-5})	(2.156×10^{-5})	(6.932×10^{-6})	(3.762×10^{-5})	(2.156×10^{-5})	(6.932×10^{-6})	(3.762×10^{-5})

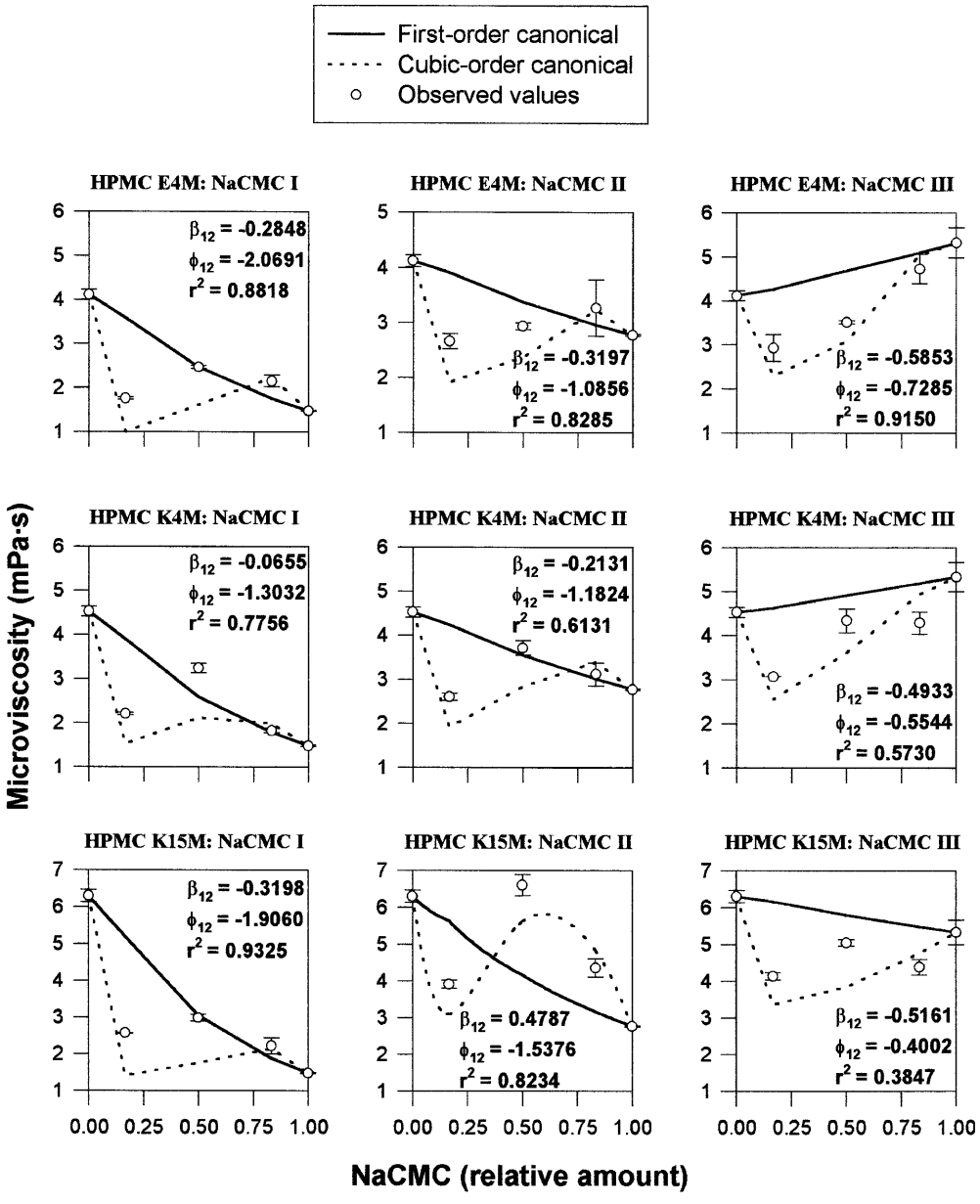

Fig. 7 Microviscosities (determined on the basis of theophylline diffusion) of the HPMC:NaCMC mixtures indicated, showing curves predicted by the first-order canonical model (i.e. the log-additivity rule) and by the second- or third-order canonical model (whichever gave the better fit)

these two polymers. For interpretation of these findings, it should be borne in mind that the macroviscosity peak reflects the formation of a three-dimensional network in which the chains of the two polymers are linked by hydrogen bonds or hydrophobic interactions. However, chain extension (leading to the adoption of a less closely coiled conformation) and interaction between hydrophobic segments may give rise to a network with higher mesh size and thus create a more hydrophilic environment, facilitating the diffusion of solute particles. This behavior is clearly different from that observed by Evertsson and Nilsson [40, 41] in mixtures of various nonionic cellulose ethers with the anionic surfactant sodium dodecyl sulfate. These authors, who used steady-state fluorescence probe techniques to determine microviscosity, observed a marked increase in microviscosity at the point of maximum rheological synergy. However, it should be borne in mind that the lipophilic character of the fluorescent marker used means that it shows lower mobility in mixed micellar aggregates than in pure surfactant micelles. Furthermore, the mechanism of interaction of the macromolecules with the surfactant differs considerably from that which would be expected for mixtures of HPMC and NaCMC.

Despite the previously mentioned disparity between the macroviscvosities and the microviscosities of our

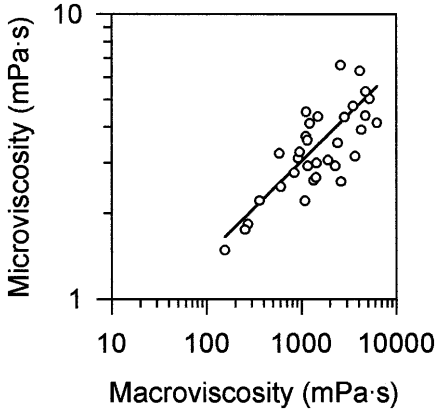

Fig. 8 Plot of the relationship between microviscosity (determined on the basis of theophylline diffusion) and macroviscosity (kinematic viscosity) of the HPMC:NaCMC mixtures indicated ($\eta_{micro} = 0.3138\eta_{micro}0.3293$; $r^2 = 0.6820$; $F_{(1,31)} = 47.98$; $\alpha < 0.01$)

HPMC:NaCMC dispersions, a clear power relationship was observed between the two parameters (Fig. 8). The goodness of fit was considerably improved if the data corresponding to the 5/6:1/6 mixture were excluded ($r^2 = 0.8105$; $F_{(1,22)} = 70.07$; $\alpha < 0.01$); this mixture showed the most extreme values of both macroviscosity and microviscosity. A similar macro/microviscosity relationship was observed in a previous study of hydroxypropylcellulose dispersions, in which microviscosity was determined both from theophylline diffusion coefficients and by dynamic light scattering using latex particles [19].

Conclusions

Some homogeneous HPMC:NaCMC mixtures have higher viscosity and elasticity than predicted by the log-additivity rule from partial concentrations, owing to the establishment of hydrophobic interactions or hydrogen bonds between the two polymers. The relative polymer proportions at which the maximum synergy is obtained, and the degree of synergy, vary depending on the polymer molecular weight and the substituent content. In mixtures containing NaCMCs of higher molecular weight and/or higher degrees of substitution, the maximum synergy in viscosity and viscous modulus is obtained with a lower proportion of NaCMC. Likewise, in mixtures containing HPMCs with a higher degree of substitution (more methoxyl groups), the degree of synergy is increased. The maximum synergy in elasticity is obtained with higher proportions of NaCMC perhaps because of the conformational changes undergone by chains at increasing concentration [35]. As a result of the chain crossover and chain expansion of both polymers, the mixtures showing the most marked synergy in viscosity are those showing lowest microviscosity (i.e. those that offer least resistance to the diffusion of theophylline). Thus, microviscosity cannot be reliably predicted from kinematic viscosity, although the two properties are related.

Acknowledgements This work was supported by grant XUGA 20315B98 (Xunta de Galicia). We thank the Xunta de Galicia for an equipment grant (DOG 04/06/97) and Dow Stade (Spain) for generous gifts of HPMC samples.

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